



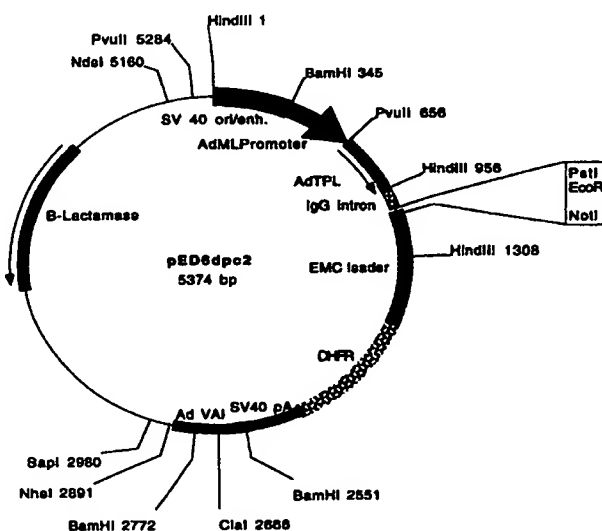
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(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of application Ser. No. 60/XXX,XXX (converted to a provisional application from non-provisional application Ser. No. 08/878,715), filed June 19, 1997, which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 185 to nucleotide 1600;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1403 to nucleotide 1600;
- 10 (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 850;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone do15_4 deposited under accession number ATCC 98468;
- 15 (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone do15_4 deposited under accession number ATCC 98468;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone do15_4 deposited under accession number ATCC 98468;
- 20 (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone do15_4 deposited under accession number ATCC 98468;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:2;
- 25 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- 30 (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 185 to nucleotide 1600; the nucleotide sequence of SEQ ID NO:1

from nucleotide 1403 to nucleotide 1600; the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 850; the nucleotide sequence of the full-length protein coding sequence of clone do15_4 deposited under accession number ATCC 98468; or the nucleotide sequence of a mature protein coding sequence of clone do15_4 deposited under
5 accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone do15_4 deposited under accession number ATCC 98468. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 222. In further preferred
10 embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:2, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having
15 biological activity, the fragment comprising the amino acid sequence from amino acid 231 to amino acid 240 of SEQ ID NO:2.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising
20 a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:2;
- (b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 222;
- 25 (c) fragments of the amino acid sequence of SEQ ID NO:2 comprising eight consecutive amino acids of SEQ ID NO:2; and
- (d) the amino acid sequence encoded by the cDNA insert of clone do15_4 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins. Preferably such
30 protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 222. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID

NO:2, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 231 to amino acid 240 of SEQ ID NO:2.

In one embodiment, the present invention provides a composition comprising an
5 isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 47 to nucleotide 2065;
- 10 (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1086 to nucleotide 1848;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone dx290_1 deposited under accession number ATCC 98468;
- 15 (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone dx290_1 deposited under accession number ATCC 98468;
- (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone dx290_1 deposited under accession number ATCC 98468;
- 20 (g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone dx290_1 deposited under accession number ATCC 98468;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;
- (i) a polynucleotide encoding a protein comprising a fragment of the
25 amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:4;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein
30 of (h) or (i) above ; and
- (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 47 to nucleotide 2065; the nucleotide sequence of SEQ ID NO:3

from nucleotide 1086 to nucleotide 1848; the nucleotide sequence of the full-length protein coding sequence of clone dx290_1 deposited under accession number ATCC 98468; or the nucleotide sequence of a mature protein coding sequence of clone dx290_1 deposited under accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone dx290_1 deposited under accession number ATCC 98468. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 312 to amino acid 600. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:4, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 331 to amino acid 340 of SEQ ID NO:4.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:4;
- (b) the amino acid sequence of SEQ ID NO:4 from amino acid 312 to amino acid 600;
- (c) fragments of the amino acid sequence of SEQ ID NO:4 comprising eight consecutive amino acids of SEQ ID NO:4; and
- (d) the amino acid sequence encoded by the cDNA insert of clone dx290_1 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 312 to amino acid 600. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:4, or a protein comprising a fragment of the amino acid sequence of

SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 331 to amino acid 340 of SEQ ID NO:4.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 107 to nucleotide 724;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID
10 NO:5 from nucleotide 218 to nucleotide 724;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 536 to nucleotide 866;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ek390_4 deposited under accession
15 number ATCC 98468;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ek390_4 deposited under accession number ATCC 98468;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ek390_4 deposited under accession number
20 ATCC 98468;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ek390_4 deposited under accession number ATCC 98468;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
- 25 (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:6;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- 30 (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 107 to nucleotide 724; the nucleotide sequence of SEQ ID NO:5 from nucleotide 218 to nucleotide 724; the nucleotide sequence of SEQ ID NO:5 from nucleotide 536 to nucleotide 866; the nucleotide sequence of the full-length protein coding
5 sequence of clone ek390_4 deposited under accession number ATCC 98468; or the nucleotide sequence of a mature protein coding sequence of clone ek390_4 deposited under accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone ek390_4 deposited under accession number ATCC 98468. In yet other preferred
10 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 6 to amino acid 92. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment preferably comprising eight (more preferably
15 twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:6, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 97 to amino acid 106 of SEQ ID NO:6.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ
20 ID NO:5.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:6;
- 25 (b) the amino acid sequence of SEQ ID NO:6 from amino acid 6 to amino acid 92;
- (c) fragments of the amino acid sequence of SEQ ID NO:6 comprising eight consecutive amino acids of SEQ ID NO:6; and
- (d) the amino acid sequence encoded by the cDNA insert of clone
30 ek390_4 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 6 to amino acid 92. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid

sequence of SEQ ID NO:6 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:6, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 97 to amino acid 106 of SEQ ID NO:6.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;
- 10 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 31 to nucleotide 1230;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 289 to nucleotide 1230;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 344 to nucleotide 1119;
- 15 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone er471_7 deposited under accession number ATCC 98468;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone er471_7 deposited under accession number ATCC 98468;
- 20 (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone er471_7 deposited under accession number ATCC 98468;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone er471_7 deposited under accession number ATCC 98468;
- 25 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:8;
- 30 (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 31 to nucleotide 1230; the nucleotide sequence of SEQ ID NO:7 from nucleotide 289 to nucleotide 1230; the nucleotide sequence of SEQ ID NO:7 from nucleotide 344 to nucleotide 1119; the nucleotide sequence of the full-length protein coding sequence of clone er471_7 deposited under accession number ATCC 98468; or the nucleotide sequence of a mature protein coding sequence of clone er471_7 deposited under accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone er471_7 deposited under accession number ATCC 98468. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8 from amino acid 111 to amino acid 363. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:8, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 195 to amino acid 204 of SEQ ID NO:8.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:8;
- (b) the amino acid sequence of SEQ ID NO:8 from amino acid 111 to amino acid 363;
- (c) fragments of the amino acid sequence of SEQ ID NO:8 comprising eight consecutive amino acids of SEQ ID NO:8; and
- (d) the amino acid sequence encoded by the cDNA insert of clone er471_7 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8 or the amino acid sequence

of SEQ ID NO:8 from amino acid 111 to amino acid 363. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:8, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 195 to amino acid 204 of SEQ ID NO:8.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 10 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 62 to nucleotide 322;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 571 to nucleotide 878;
- 15 (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone fs40_3 deposited under accession number ATCC 98468;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone fs40_3 deposited under accession number ATCC 98468;
- 20 (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone fs40_3 deposited under accession number ATCC 98468;
- (g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone fs40_3 deposited under accession number ATCC 98468;
- 25 (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:10;
- 30 (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 62 to nucleotide 322; the nucleotide sequence of SEQ ID NO:9 from nucleotide 571 to nucleotide 878; the nucleotide sequence of the full-length protein coding sequence of clone fs40_3 deposited under accession number ATCC 98468; or the nucleotide sequence of a mature protein coding sequence of clone fs40_3 deposited under accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone fs40_3 deposited under accession number ATCC 98468. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:10, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 38 to amino acid 47 of SEQ ID NO:10.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
- (b) fragments of the amino acid sequence of SEQ ID NO:10 comprising eight consecutive amino acids of SEQ ID NO:10; and
- (c) the amino acid sequence encoded by the cDNA insert of clone fs40_3 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:10, or a protein comprising a fragment of the amino acid sequence of

SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 38 to amino acid 47 of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 5 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 43 to nucleotide 1671;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID
10 NO:11 from nucleotide 112 to nucleotide 1671;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 224 to nucleotide 679;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ga63_6 deposited under accession number
15 ATCC 98468;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ga63_6 deposited under accession number ATCC 98468;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ga63_6 deposited under accession number ATCC
20 98468;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ga63_6 deposited under accession number ATCC 98468;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
- 25 (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:12;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- 30 (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 43 to nucleotide 1671; the nucleotide sequence of SEQ ID NO:11 from nucleotide 112 to nucleotide 1671; the nucleotide sequence of SEQ ID NO:11 from nucleotide 224 to nucleotide 679; the nucleotide sequence of the full-length protein coding
5 sequence of clone ga63_6 deposited under accession number ATCC 98468; or the nucleotide sequence of a mature protein coding sequence of clone ga63_6 deposited under accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone ga63_6 deposited under accession number ATCC 98468. In yet other preferred embodiments,
10 the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 62 to amino acid 212. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment preferably comprising eight (more preferably twenty,
15 most preferably thirty) consecutive amino acids of SEQ ID NO:12, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 266 to amino acid 275 of SEQ ID NO:12.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ
20 ID NO:11.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:12;
- 25 (b) the amino acid sequence of SEQ ID NO:12 from amino acid 62 to amino acid 212;
- (c) fragments of the amino acid sequence of SEQ ID NO:12 comprising eight consecutive amino acids of SEQ ID NO:12; and
- (d) the amino acid sequence encoded by the cDNA insert of clone
30 ga63_6 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 62 to amino acid 212. In further preferred embodiments, the present invention provides a protein comprising a fragment of the

amino acid sequence of SEQ ID NO:12 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:12, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid
5 sequence from amino acid 266 to amino acid 275 of SEQ ID NO:12.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- 10 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 17 to nucleotide 523;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 77 to nucleotide 523;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID
15 NO:13 from nucleotide 1 to nucleotide 392;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone gm335_4 deposited under accession number ATCC 98468;
- (f) a polynucleotide encoding the full-length protein encoded by the
20 cDNA insert of clone gm335_4 deposited under accession number ATCC 98468;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone gm335_4 deposited under accession number ATCC 98468;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA
25 insert of clone gm335_4 deposited under accession number ATCC 98468;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment
30 comprising eight consecutive amino acids of SEQ ID NO:14;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 17 to nucleotide 523; the nucleotide sequence of SEQ ID NO:13 from nucleotide 77 to nucleotide 523; the nucleotide sequence of SEQ ID NO:13 from nucleotide 1 to nucleotide 392; the nucleotide sequence of the full-length protein coding sequence of clone gm335_4 deposited under accession number ATCC 98468; or the nucleotide sequence of a mature protein coding sequence of clone gm335_4 deposited under accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone gm335_4 deposited under accession number ATCC 98468. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 125. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:14, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 79 to amino acid 88 of SEQ ID NO:14.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:14;
- (b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 125;
- (c) fragments of the amino acid sequence of SEQ ID NO:14 comprising eight consecutive amino acids of SEQ ID NO:14; and
- (d) the amino acid sequence encoded by the cDNA insert of clone gm335_4 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14 or the amino acid sequence

of SEQ ID NO:14 from amino acid 1 to amino acid 125. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID
5 NO:14, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 79 to amino acid 88 of SEQ ID NO:14.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- 10 (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 2 to nucleotide 991;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID
15 NO:15 from nucleotide 62 to nucleotide 991;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 2 to nucleotide 504;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone hy370_9 deposited under accession
20 number ATCC 98468;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone hy370_9 deposited under accession number ATCC 98468;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone hy370_9 deposited under accession number
25 ATCC 98468;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone hy370_9 deposited under accession number ATCC 98468;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;
- 30 (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:16;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

5 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 2 to nucleotide 991; the nucleotide sequence of SEQ ID NO:15 from nucleotide 62 to nucleotide 991; the nucleotide sequence of SEQ ID NO:15 from nucleotide 2 to nucleotide 504; the nucleotide sequence of the full-length protein coding sequence of clone hy370_9 deposited under accession number ATCC 98468; or the
10 nucleotide sequence of a mature protein coding sequence of clone hy370_9 deposited under accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone hy370_9 deposited under accession number ATCC 98468. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein
15 comprising the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 167. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:16, or a
20 polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 160 to amino acid 169 of SEQ ID NO:16.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

25 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
- (b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to
30 amino acid 167;
- (c) fragments of the amino acid sequence of SEQ ID NO:16 comprising eight consecutive amino acids of SEQ ID NO:16; and
- (d) the amino acid sequence encoded by the cDNA insert of clone hy370_9 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 167. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid
5 sequence of SEQ ID NO:16 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:16, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 160 to amino acid 169 of SEQ ID NO:16.

10 In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

15 (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 77 to nucleotide 616;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 164 to nucleotide 616;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 415;

20 (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ie47_4 deposited under accession number ATCC 98468;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ie47_4 deposited under accession number ATCC 98468;

25 (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ie47_4 deposited under accession number ATCC 98468;

(h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ie47_4 deposited under accession number ATCC 98468;

30 (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:18;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

5 (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 77 to nucleotide 616; the nucleotide sequence of SEQ ID NO:17 from nucleotide 164 to nucleotide 616; the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 415; the nucleotide sequence of the full-length protein coding sequence of clone ie47_4 deposited under accession number ATCC 98468; or the nucleotide sequence of a mature protein coding sequence of clone ie47_4 deposited under accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone ie47_4 deposited under accession number ATCC 98468. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 113. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:18, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 85 to amino acid 94 of SEQ ID NO:18.

25 Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

- 30 (a) the amino acid sequence of SEQ ID NO:18;
- (b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 113;
- (c) fragments of the amino acid sequence of SEQ ID NO:18 comprising eight consecutive amino acids of SEQ ID NO:18; and

(d) the amino acid sequence encoded by the cDNA insert of clone ie47_4 deposited under accession number ATCC 98468; the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18 or the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 113. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:18, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 85 to amino acid 94 of SEQ ID NO:18.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 564 to nucleotide 2813;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 705 to nucleotide 2813;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 793 to nucleotide 1628;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone s195_10 deposited under accession number ATCC 98468;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone s195_10 deposited under accession number ATCC 98468;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone s195_10 deposited under accession number ATCC 98468;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone s195_10 deposited under accession number ATCC 98468;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:20;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

10 Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:19 from nucleotide 564 to nucleotide 2813; the nucleotide sequence of SEQ ID NO:19 from nucleotide 705 to nucleotide 2813; the nucleotide sequence of SEQ ID NO:19 from nucleotide 793 to nucleotide 1628; the nucleotide sequence of the full-length protein coding sequence of clone s195_10 deposited under accession number ATCC 98468; or the
15 nucleotide sequence of a mature protein coding sequence of clone s195_10 deposited under accession number ATCC 98468. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone s195_10 deposited under accession number ATCC 98468. In yet other preferred
20 embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20 from amino acid 78 to amino acid 355. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:20, or a
25 polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 370 to amino acid 379 of SEQ ID NO:20.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:19.

30 In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 78 to amino acid 355;

(c) fragments of the amino acid sequence of SEQ ID NO:20 comprising eight consecutive amino acids of SEQ ID NO:20; and

5 (d) the amino acid sequence encoded by the cDNA insert of clone s195_10 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:20 or the amino acid sequence of SEQ ID NO:20 from amino acid 78 to amino acid 355. In further preferred
10 embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) consecutive amino acids of SEQ ID NO:20, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid
15 sequence from amino acid 370 to amino acid 379 of SEQ ID NO:20.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or
20 modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

25 (b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which
30 specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

5

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide
10 sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature forms) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by
15 expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal
20 sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

25 Clone "do15_4"

A polynucleotide of the present invention has been identified as clone "do15_4". do15_4 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer
30 analysis of the amino acid sequence of the encoded protein. do15_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "do15_4 protein").

The nucleotide sequence of do15_4 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted

amino acid sequence of the do15_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 394 to 406 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 407, or are a transmembrane domain.

5 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone do15_4 should be approximately 1900 bp.

 The nucleotide sequence disclosed herein for do15_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. do15_4 demonstrated at least some similarity with sequences
10 identified as AA113909 (zm80f12.r1 Stratagene neuroepithelium (#937231) Homo sapiens cDNA clone 531983 5'), AA189888 (mu55h06.r1 Soares mouse lymph node NbMLN Mus musculus cDNA clone 643355 5'), and U52052 (Human S6 A-8 mRNA expressed in chromosome 6-suppressed melanoma cells). Based upon sequence similarity, do15_4 proteins and each similar protein or peptide may share at least some activity.

15

Clone "dx290_1"

 A polynucleotide of the present invention has been identified as clone "dx290_1". dx290_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was
20 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. dx290_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "dx290_1 protein").

 The nucleotide sequence of dx290_1 as presently determined is reported in SEQ
25 ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the dx290_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4.

 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone dx290_1 should be approximately 2300 bp.

30 The nucleotide sequence disclosed herein for dx290_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. dx290_1 demonstrated at least some similarity with the sequence identified as AA064383 (ml47h02.r1 Stratagene mouse testis (#937308) Mus

musculus cDNA clone 515187 5'). Based upon sequence similarity, dx290_1 proteins and each similar protein or peptide may share at least some activity.

Clone "ek390_4"

5 A polynucleotide of the present invention has been identified as clone "ek390_4". ek390_4 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ek390_4 is a full-length clone,
10 including the entire coding sequence of a secreted protein (also referred to herein as "ek390_4 protein").

The nucleotide sequence of ek390_4 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ek390_4 protein corresponding to the foregoing
15 nucleotide sequence is reported in SEQ ID NO:6. Amino acids 25 to 37 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 38, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ek390_4 should be approximately 1000 bp.

20 The nucleotide sequence disclosed herein for ek390_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. ek390_4 demonstrated at least some similarity with sequences identified as AA075783 (zm89h02.r1 Stratagene ovarian cancer (#937219) Homo sapiens cDNA clone 545139 5'), AA427538 (zw32g04.r1 Soares ovary tumor NbHOT Homo sapiens cDNA clone 771030 5'), AA427539 (zw32g04.s1 Soares ovary tumor NbHOT Homo sapiens cDNA clone 771030 3'), AA453353 (zx47a06.r1 Soares testis NHT Homo sapiens cDNA clone 795346 5'), C20637 (HUMGS0004639, Human Gene Signature, 3'-directed cDNA sequence), R74326 (yl01c07.s1 Homo sapiens cDNA clone 156972 3'), R74420 (yl01c07.r1 Homo sapiens cDNA clone 156972 5'), T22914 (Human gene
25 signature), U41197 (Human [TTTC]10 short tandem repeat polymorphism UM65, D17S1340), and X58237 (Human mRNA for anti-lectin antibody epitope (clone p36/8-6)). Based upon sequence similarity, ek390_4 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential
30

transmembrane domain within the ek390_4 protein sequence centered around amino acid 160 of SEQ ID NO:6. The nucleotide sequence of ek390_4 indicates that it may contain GGGA repeat sequences.

5 Clone "er471_7"

A polynucleotide of the present invention has been identified as clone "er471_7". er471_7 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer
10 analysis of the amino acid sequence of the encoded protein. er471_7 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "er471_7 protein").

The nucleotide sequence of er471_7 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the predicted
15 amino acid sequence of the er471_7 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8. Amino acids 74 to 86 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 87, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone
20 er471_7 should be approximately 2250 bp.

The nucleotide sequence disclosed herein for er471_7 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. er471_7 demonstrated at least some similarity with sequences identified as AA039137 (mi98h06.r1 Soares mouse embryo NbME13.5 14.5 Mus
25 musculus cDNA clone 474683 5'), AA066962 (mm38g05.r1 Stratagene mouse melanoma (#937312) Mus musculus cDNA clone 523832 5'), AA189170 (zq47h05.s1 Stratagene hNT neuron (#937233) Homo sapiens cDNA clone 632889 3'), AA609188 (af12c10.s1 Soares testis NHT Homo sapiens cDNA clone 1031442 3'), and W07704 (zb02e02.r1 Soares fetal lung NbHL19W Homo sapiens cDNA clone 300890 5' similar to
30 SW:YN66_YEAST P40164 HYPOTHETICAL 98.1 KD PROTEIN IN SPX19-GCR2 INTERGENIC REGION). The predicted amino acid sequence disclosed herein for er471_7 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted er471_7 protein demonstrated at least

some similarity to sequences identified as AF016448 (Cosmid F41E6 [Caenorhabditis elegans]) and L08407 (collagen type XVII [Mus musculus]). Based upon sequence similarity, er471_7 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts three potential transmembrane domains within the er471_7 protein sequence, centered around amino acids 40, 80, and 110 of SEQ ID NO:8, respectively.

Clone "fs40_3"

A polynucleotide of the present invention has been identified as clone "fs40_3". fs40_3 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. fs40_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "fs40_3 protein").

The nucleotide sequence of fs40_3 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the fs40_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone fs40_3 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for fs40_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. fs40_3 demonstrated at least some similarity with sequences identified as AA411142 (zt37g01.r1 Soares ovary tumor NbHOT Homo sapiens cDNA clone 724560 5'), AA412527 (zu12a03.s1 Soares testis NHT Homo sapiens cDNA clone 731596 3'), AA565855 (nj32d09.s1 NCI_CGAP_AA1 Homo sapiens cDNA clone IMAGE:994193), H17042 (ym39f12.s1 Homo sapiens cDNA clone 50584 3'), and T33280 (EST57284 Homo sapiens cDNA 3' end similar to None). Based upon sequence similarity, fs40_3 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the fs40_3 protein sequence at the C-terminus of SEQ ID NO:10.

Clone "ga63_6"

A polynucleotide of the present invention has been identified as clone "ga63_6". ga63_6 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was
5 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ga63_6 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "ga63_6 protein").

The nucleotide sequence of ga63_6 as presently determined is reported in SEQ ID
10 NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ga63_6 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Amino acids 11 to 23 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 24, or are a transmembrane domain.

15 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ga63_6 should be approximately 2300 bp.

The nucleotide sequence disclosed herein for ga63_6 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. ga63_6 demonstrated at least some similarity with sequences
20 identified as AA405433 (zu13h10.r1 Soares testis NHT Homo sapiens cDNA clone 731779 5'similar to TR G474970 G474970 SP32 PRECURSOR), AA406076 (zu67c02.s1 Soares testis NHT Homo sapiens cDNA clone 743042 3' similar to TR:G475021 G475021 SP32 PRECURSOR), AA424694 (zu13h10.s1 Soares testis NHT Homo sapiens cDNA clone 731779 3' similar to TR G475021 G475021 SP32 PRECURSOR; contains element
25 TAR1 repetitive element), D16200 (Pig mRNA for sp32, partial sequence), D16203 (Guinea pig mRNA for sp32, complete cds), and D17573 (Mouse mRNA for proacrosin-binding protein (sp32), complete cds). The predicted amino acid sequence disclosed herein for ga63_6 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted ga63_6 protein
30 demonstrated at least some similarity to sequences identified as D16200 (sp32 precursor [Sus scrofa]), and D17574 (alternative splicing product for proacrosin-binding protein (sp32) [Mus musculus]). The sp32 protein is found in the acrosomal vesicle of sperm, which is involved in egg-sperm fusion in fertilization. This protein is initially synthesized

as a 61-kDa precursor protein with a putative signal peptide at the amino terminus. The carboxyl-terminal half of the precursor molecule corresponds to the mature sp32 protein. Thus, sp32 is produced by post-translational modification of the precursor. The binding of sp32 to proacrosin may be involved in packaging the acrosin zymogen into the acrosomal matrix. (Baba *et al.*, 1994, *J. Biol. Chem.* **269** (13): 10133-10140, which is incorporated by reference herein). Based upon sequence similarity, ga63_6 proteins and each similar protein or peptide may share at least some activity.

Clone "gm335_4"

A polynucleotide of the present invention has been identified as clone "gm335_4". gm335_4 was isolated from a human adult uterus cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. gm335_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "gm335_4 protein").

The nucleotide sequence of gm335_4 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the gm335_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14. Amino acids 8 to 20 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 21, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone gm335_4 should be approximately 800 bp.

The nucleotide sequence disclosed herein for gm335_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. gm335_4 demonstrated at least some similarity with sequences identified as AA055367 (zf20b05.r1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 377457 5'), AC002389 (Human DNA from chromosome 19 specific cosmid R28461, genomic sequence, complete sequence), W08522 (mb46h10.r1 Soares mouse p3NMF19.5 Mus musculus cDNA clone 332515 5'), and X93916 (S.scrofa mRNA (clone VIB11; expressed sequence tag)). Based upon sequence similarity, gm335_4 proteins and each similar protein or peptide may share at least some activity.

Clone "hy370_9"

A polynucleotide of the present invention has been identified as clone "hy370_9". hy370_9 was isolated from a human adult trachea cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was
5 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. hy370_9 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "hy370_9 protein").

The nucleotide sequence of hy370_9 as presently determined is reported in SEQ
10 ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the hy370_9 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16. Amino acids 8 to 20 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 21, or are a transmembrane domain.

15 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone hy370_9 should be approximately 1200 bp.

The nucleotide sequence disclosed herein for hy370_9 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. hy370_9 demonstrated at least some similarity with the
20 sequence identified as AA763313 (vv89h07.r1 Stratagene mouse skin (#937313) Mus musculus cDNA clone 1229629 5'). Based upon sequence similarity, hy370_9 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts an additional potential transmembrane domain within the hy370_9 protein sequence centered around amino acid 140 of SEQ ID NO:16.

25

Clone "ie47_4"

A polynucleotide of the present invention has been identified as clone "ie47_4". ie47_4 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was
30 identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ie47_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "ie47_4 protein").

The nucleotide sequence of ie47_4 as presently determined is reported in SEQ ID NO:17. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ie47_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18. Amino acids 17 to 29 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 30, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ie47_4 should be approximately 2300 bp.

The nucleotide sequence disclosed herein for ie47_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. ie47_4 demonstrated at least some similarity with sequences identified as AA071953 (mf17h08.r1 Life Tech mouse brain Mus musculus cDNA clone 405375 5' similar to TR G304421 G304421 SILENCER ELEMENT), AA207250 (zq82d05.s1 Stratagene hNT neuron (#937233) Homo sapiens cDNA clone 648105 3' similar to TR G304421 G304421 SILENCER ELEMENT), L14938 (Chicken SCG10 protein mRNA, complete cds), L20260 (Mouse SCG10 gene sequence), R49053 (yg58c05.s1 Homo sapiens cDNA clone 37017 3'), S82024 (SCG10 neuron-specific growth-associated protein/stathmin homolog [human, embryo, mRNA]), T25428 (Human gene signature HUMGS07594, T25428 standard; cDNA to mRNA), W54204 (md04a12.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA clone 367390 5' similar to SW:SCGB_XENLA Q09002 SCG10 PROTEIN HOMOLOG A), X71433 (X. laevis SCG10 mRNA), and Z99916 (Human DNA sequence *** SEQUENCING IN PROGRESS *** from clone 221G9; HTGS phase 1). The predicted amino acid sequence disclosed herein for ie47_4 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted ie47_4 protein demonstrated at least some similarity to sequences identified as L14938 (SCG10 protein [Gallus gallus]) and S82024 (SCG10 neuron-specific growth-associated protein/stathmin homolog [human, embryo, Peptide] [Homo sapiens]). SCG10 protein is considered to be a membrane-bound protein present in neural growth cones and developing neurons (Maucuer *et al.*, 1993, *J. Biol. Chem.* 268: 16420-16429; Stein *et al.*, 1988, *Neuron* 1:463-476; which are incorporated by reference herein). Based upon sequence similarity, ie47_4 proteins and each similar protein or peptide may share at least some activity.

Clone "s195_10"

A polynucleotide of the present invention has been identified as clone "s195_10". s195_10 was isolated from a human adult neural tissue cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or
 5 was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. s195_10 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "s195_10 protein").

The nucleotide sequence of s195_10 as presently determined is reported in SEQ ID
 10 NO:19. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the s195_10 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:20. Amino acids 35 to 47 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 48, or are a transmembrane domain.

15 The EcoRI/NotI restriction fragment obtainable from the deposit containing clone s195_10 should be approximately 3500 bp.

The nucleotide sequence disclosed herein for s195_10 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. s195_10 demonstrated at least some similarity with sequences
 20 identified as AA113800 (zn65b05.s1 Stratagene HeLa cell s3 937216 Homo sapiens cDNA clone 563025 3' similar to TR:G600018 G600018 SSM4P), AA114062 (zn65b05.r1 Stratagene HeLa cell s3 937216 Homo sapiens cDNA clone 563025 5'), AA280316 (zt10f06.s1 Soares NbHTGBC Homo sapiens cDNA clone 712739 3'), AF009301 (Homo sapiens TEB4 protein mRNA, complete cds), N70344 (za60f10.s1 Homo sapiens cDNA
 25 clone 296971 3'), R60474 (yh13g07.r1 Homo sapiens cDNA clone 43058 5'), and T26266 (standard; cDNA to mRNA; 148 BP, Human gene signature HUMGS08505). The predicted amino acid sequence disclosed herein for s195_10 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted s195_10 protein demonstrated at least some similarity to sequences
 30 identified as AF009301 (TEB4 protein [Homo sapiens]), X76715 (SSM4 gene product [Saccharomyces cerevisiae]), Z46861 (Ssm4p [Saccharomyces cerevisiae]), and Z47047 (Ssm4p [Saccharomyces cerevisiae]). Based upon sequence similarity, s195_10 proteins and each similar protein or peptide may share at least some activity. The TopPredII

computer program predicts eleven additional potential transmembrane domains within the s195_10 protein sequence, centered around amino acids 130, 170, 210, 260, 320, 470, 520, 560, 600, 650, and 690 of SEQ ID NO:20, respectively. The nucleotide sequence of s195_10 indicates that it may contain a simple GAA repeat region.

5

Deposit of Clones

Clones do15_4, dx290_1, ek390_4, er471_7, fs40_3, ga63_6, gm335_4, hy370_9, ie47_4, and s195_10 were deposited on June 19, 1997 with the American Type Culture Collection (10801 University Boulevard, Manassas, Virginia 20110-2209 U.S.A.) as an original deposit under the Budapest Treaty and were given the accession number ATCC 98468, from which each clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b), and the term of the deposit will comply with 37 C.F.R. § 1.806.

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Figures 1A and 1B, respectively. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* 19: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of an

oligonucleotide probe that was used to isolate or to sequence each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

	<u>Clone</u>	<u>Probe Sequence</u>
5	do15_4	SEQ ID NO:21
	dx290_1	SEQ ID NO:22
	ek390_4	SEQ ID NO:23
	er471_7	SEQ ID NO:24
	fs40_3	SEQ ID NO:25
10	ga63_6	SEQ ID NO:26
	gm335_4	SEQ ID NO:27
	hy370_9	SEQ ID NO:28
	ie47_4	SEQ ID NO:29
	s195_10	SEQ ID NO:30

15

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite) (Glen Research, cat. no. 10-1953)).

20

The design of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- 25 (b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with γ - ^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately $4\text{e}+6$ dpm/pmole.

30

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 μ l of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 μ g/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in
5 fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 μ g/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

10 Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 μ g/ml of yeast RNA, and 10 mM EDTA (approximately
15 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes.
20 A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated
25 using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example,
30 as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to

the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

5 The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form(s) of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or
10 other host cell. The sequence(s) of the mature form(s) of the protein may also be determinable from the amino acid sequence of the full-length form.

 The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are
15 derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed
20 herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

25 Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* **15**(7): 250-254; Lavarosky *et al.*, 1997,
30 *Biochem. Mol. Med.* **62**(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* **58**: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided.

Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that

shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologues of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or
5 polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide. Preferably, polynucleotide species homologues have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with
10 the given polynucleotide, and protein species homologues have at least 30% sequence identity (more preferably, at least 45% identity; most preferably at least 60% identity) with the given protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides or the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Species homologues may be isolated and identified by making suitable probes or primers from
15 the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologues are those isolated from mammalian species. Most preferably, species homologues are those isolated from certain mammalian species such as, for example, *Pan troglodytes*, *Gorilla gorilla*, *Pongo pygmaeus*, *Hylobates concolor*, *Macaca mulatta*, *Papio papio*, *Papio hamadryas*, *Cercopithecus aethiops*, *Cebus capucinus*,
20 *Aotus trivirgatus*, *Sanguinus oedipus*, *Microcebus murinus*, *Mus musculus*, *Rattus norvegicus*, *Cricetulus griseus*, *Felis catus*, *Mustela vison*, *Canis familiaris*, *Oryctolagus cuniculus*, *Bos taurus*, *Ovis aries*, *Sus scrofa*, and *Equus caballus*, for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species
25 (O'Brien and Seuáñez, 1988, *Ann. Rev. Genet.* 22: 323-351; O'Brien *et al.*, 1993, *Nature Genetics* 3:103-112; Johansson *et al.*, 1995, *Genomics* 25: 682-690; Lyons *et al.*, 1997, *Nature Genetics* 15: 47-56; O'Brien *et al.*, 1997, *Trends in Genetics* 13(10): 393-399; Carver and Stubbs, 1997, *Genome Research* 7:1123-1137; all of which are incorporated by reference herein).

The invention also encompasses allelic variants of the disclosed polynucleotides
30 or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotides which also encode proteins which are identical or have significantly similar sequences to those encoded by the disclosed polynucleotides. Preferably, allelic variants have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90%

identity) with the given polynucleotide, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps. Allelic variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and
5 screening a suitable nucleic acid source from individuals of the appropriate species.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides that hybridize under reduced stringency conditions, more preferably stringent conditions, and most preferably highly
10 stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) [‡]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
5	A	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
	B	<50	T _B *; 1xSSC	T _B *; 1xSSC
	C	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
	D	<50	T _D *; 1xSSC	T _D *; 1xSSC
	E	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
	F	<50	T _F *; 1xSSC	T _F *; 1xSSC
10	G	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
	H	<50	T _H *; 4xSSC	T _H *; 4xSSC
	I	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
	J	<50	T _J *; 4xSSC	T _J *; 4xSSC
	K	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
	L	<50	T _L *; 2xSSC	T _L *; 2xSSC
15	M	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
	N	<50	T _N *; 6xSSC	T _N *; 6xSSC
	O	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
	P	<50	T _P *; 6xSSC	T _P *; 6xSSC
	Q	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
	R	<50	T _R *; 4xSSC	T _R *; 4xSSC

[‡]: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

[†]: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6(log₁₀[Na⁺]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds.,

5 John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or
10 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an
15 expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably
20 linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the
25 protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

30 Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant

methyle or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance
5 with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

10 The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith,
15 including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally
20 provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another
25 amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be
30 expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, those described in Gyuris *et al.*, 1993, *Cell* 75: 791-803 and in Rossi *et al.*, 1997, *Proc. Natl. Acad. Sci. USA* 94: 8405-8410, all of which are incorporated by reference herein) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine

levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is

evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

- 5 The activity of a protein of the invention may, among other means, be measured by the following methods:

 Assays for T-cell or thymocyte proliferation include without limitation those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-
10 Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

- 15 Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ , Schreiber, R.D. In *Current Protocols in*
20 *Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

- Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons,
25 Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau et al., *Nature* 336:690-692, 1988; Greenberger et al., *Proc. Natl. Acad. Sci. U.S.A.* 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:1857-1861, 1986; Measurement of human
30 Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for

example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or

tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of

viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface.

Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

10 The activity of a protein of the invention may, among other means, be measured by the following methods:

 Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Herrmann et al., *J. Immunol.* 128:1968-1974, 1982; Handa et al., *J. Immunol.* 135:1564-1572, 1985; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Takai et al., *J. Immunol.* 140:508-512, 1988; Herrmann et al., *Proc. Natl. Acad. Sci. USA* 78:2488-2492, 1981; Herrmann et al., *J. Immunol.* 128:1968-1974, 1982; Handa et al., *J. Immunol.* 135:1564-1572, 1985; Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bowman et al., *J. Virology* 61:1992-1998; Takai et al., *J. Immunol.* 140:508-512, 1988; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Brown et al., *J. Immunol.* 153:3079-3092, 1994.

25 Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, *J. Immunol.* 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

30 Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-

Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity)

useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. *Cellular Biology* 15:141-151, 1995; Keller et al., *Molecular and Cellular Biology* 13:473-486, 1993; McClanahan et al., *Blood* 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., *Proc. Natl. Acad. Sci. USA* 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., *Experimental Hematology* 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 163-179,

Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

5 Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

10 A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De*
15 *novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment
20 to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory
25 processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of
30 tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue

formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon-
5 or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also
10 include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and
15 traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager
20 syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

25 Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example,
30 pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting
5 differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described
10 in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in:
Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year
15 Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related
20 activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals
25 and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example,
30 United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

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Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells.

10 Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses
15 against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population
20 of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent
25 chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene
30 Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al. Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

10 The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 15 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

30 The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and

Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 5 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in 10 the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat 15 inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting 20 from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major 25 roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

30 The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the

first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

5 E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to
10 their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention
15 encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue
20 in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and
25 polynucleotides of the present invention encoding such proteins, can be used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the
30 cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used

to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides
5 encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

10 Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or
15 tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

20 Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height,
25 weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein,
30 carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic

lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen

5 in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

10 A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term

15 "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11,

20 IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention,

25 or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

30 A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be

administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred

pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The
5 pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone.
10 Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not
15 increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1mg to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous
20 therapy using the pharmaceutical composition of the present invention.
25

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the
30 carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal

antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting
5 and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When
10 administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also
15 optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the
20 developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular
25 application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins
30 or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-

aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns.

- 5 In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, 10 ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 15 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

20 In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), and insulin-like growth factor (IGF).

25 The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering 30 various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in

the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline
5 labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without
10 limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

15 Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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- 15 (ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES
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- (iii) NUMBER OF SEQUENCES: 30
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30 (A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- 35 (vi) CURRENT APPLICATION DATA:
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(B) FILING DATE:
(C) CLASSIFICATION:
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(2) INFORMATION FOR SEQ ID NO:1:

- 50 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1748 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
55 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GTTTAGTGAT ACGACACAAG ATCGGGAGAT TTTTGATCAC CATACTGAAG AGGATATAGA 60
 10 TAAAAGTGCT AACAGTGTAT TGATAAAAAA CCTGAGCAGG ACCCCATCTA GTTGCAGCAG 120
 CTCTCTGGAT TCAATCAAGG CTGATGGGAC CTCTCTGGAC TTCAGCACTT ACCGCAGTAG 180
 15 TCAAAATGGAA TCACAGTTTC TCAGAGATAC TATTTGTGAA GAGAGCTTGA GGGAGAAACT 240
 CCAAGATGGG AGAATAACAA TAAGGGAGTT CTTTATACTT CTCCAGGTCC ACATCTTGAT 300
 ACAGAAACCC CGACAGAGCA ATCTCCCAGG CAATTTTACT GTAAACACAC CACCTACTCC 360
 20 AGAAGACCTG ATGTTAAGTC AATATGTTTA CCGACCCAAG ATACAGATTT ATAGAGAAGA 420
 TTGTGAGGCT CGTCGCCAAA AGATTGAAGA ATTAAAGCTT TCTGCATCGA ACCAAGATAA 480
 25 GCTGTTGGTT GATATAAATA AGAACCTGTG GGAAAAATG AGACACTGCT CTGACAAAGA 540
 GCTGAAGGCC TTTGGAATTT ATCTTAACAA AATAAAGTCA TGTTTTACCA AGATGACTAA 600
 AGTCTTCACT CACCAAGGAA AAGTGGCTCT GTATGGCAAG CTGGTGCAGT CAGCTCAGAA 660
 30 TGAGAGGGAG AAACCTCAAA TAAAGATAGA TGAGATGGAT AAAATACTTA AGAAGATCGA 720
 TAACTGCCTC ACTGAGATGG AAACAGAAAC TAAGAATTTG GAGGATGAAG AGAAAAACAA 780
 35 TCCTGTGGAA GAATGGGATT CTGAAATGAG AGCTGCAGAA AAAGAATTGG AACAGCTGAA 840
 AACTGAAGAG GAGGAGCTTC AAAGAAATCT CTTAGAACTG GAGGTACCAA AAGAGCAGAC 900
 CCTTGCTCAA ATAGACTTTA TGCAAAAACA AAGAAATAGA ACTGAAGAGC TACTGGATCA 960
 40 GTTGAGCTTG TCTGAGTGGG ATGTCGTTGA GTGGAGTGAT GATCAAGCTG TATTCACCTT 1020
 TGTTTATGAC ACGATACAAC TCACCATCAC CTTTGAAGAG TCAGTTGTTG GTTTCCCTTT 1080
 45 CCTGGACAAG CGTTATAGGA AGATTGTTGA TGTCAATTTT CAATCTCTGT TAGATGAGGA 1140
 TCAAGCTCCT CCTTCCTCCC TTTTAGTTCA TAAGCTTATT TTCCAGTACG TTGAAGAAAA 1200
 GGAATCCTGG AAGAAGACAT GTACAACCCA GCATCAGTTA CCCAAGATGC TTGAAGAATT 1260
 50 CTCAGTGGTA GTGCACCATT GCAGACTCCT TGGAGAGGAG ATTGAGTATT TAAAGAGATG 1320
 GGGACCAAAT TATAACCTAA TGAACATAGA TATTAATAAT AATGAATTGA GACTTTTATT 1380
 55 CTCTAGCTCC GCAGCATTTG CAAAGTTTGA AATAACTTTG TTTCTCTCAG CCTATTATCC 1440

ATCTGTACCA TTACCTTCCA CCATTTCAGAA TCACGTTGGG AACACTAGCC AAGATGATAT 1500
 TGCTACCATT CTATCTAAAG TGCCACTGGA GAACAACCTAC CTGAAGAATG TAGTCAAGCA 1560
 5 AATTTACCAA GATCTGTTTC AGGACTGCCA TTTCTACCAC TAGACCCTTG GACCACCATT 1620
 GGAACAACCA AGCAGAATGT ACTTGATATT ATTTTCAGGGT CCCATTGCTG TTCAGCCTTT 1680
 10 GTTTTTACGT CATTACAAGC TGAGTAAAAT TCCTTCTGAT GATGTTATAA AAAAAAAAAA 1740
 AAAAAAAAAA 1748

(2) INFORMATION FOR SEQ ID NO:2:

15 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 472 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Glu Ser Gln Phe Leu Arg Asp Thr Ile Cys Glu Glu Ser Leu Arg
 1 5 10 15
 30 Glu Lys Leu Gln Asp Gly Arg Ile Thr Ile Arg Glu Phe Phe Ile Leu
 20 25 30
 35 Leu Gln Val His Ile Leu Ile Gln Lys Pro Arg Gln Ser Asn Leu Pro
 35 40 45
 Gly Asn Phe Thr Val Asn Thr Pro Pro Thr Pro Glu Asp Leu Met Leu
 50 55 60
 40 Ser Gln Tyr Val Tyr Arg Pro Lys Ile Gln Ile Tyr Arg Glu Asp Cys
 65 70 75 80
 Glu Ala Arg Arg Gln Lys Ile Glu Glu Leu Lys Leu Ser Ala Ser Asn
 85 90 95
 45 Gln Asp Lys Leu Leu Val Asp Ile Asn Lys Asn Leu Trp Glu Lys Met
 100 105 110
 Arg His Cys Ser Asp Lys Glu Leu Lys Ala Phe Gly Ile Tyr Leu Asn
 115 120 125
 50 Lys Ile Lys Ser Cys Phe Thr Lys Met Thr Lys Val Phe Thr His Gln
 130 135 140
 55 Gly Lys Val Ala Leu Tyr Gly Lys Leu Val Gln Ser Ala Gln Asn Glu

	145		150		155		160
	Arg Glu Lys Leu Gln Ile Lys Ile Asp Glu Met Asp Lys Ile Leu Lys						
5			165		170		175
	Lys Ile Asp Asn Cys Leu Thr Glu Met Glu Thr Glu Thr Lys Asn Leu						
			180		185		190
10	Glu Asp Glu Glu Lys Asn Asn Pro Val Glu Glu Trp Asp Ser Glu Met						
			195		200		205
	Arg Ala Ala Glu Lys Glu Leu Glu Gln Leu Lys Thr Glu Glu Glu Glu						
			210		215		220
15	Leu Gln Arg Asn Leu Leu Glu Leu Glu Val Pro Lys Glu Gln Thr Leu						
			225		230		235
	Ala Gln Ile Asp Phe Met Gln Lys Gln Arg Asn Arg Thr Glu Glu Leu						
			245		250		255
20	Leu Asp Gln Leu Ser Leu Ser Glu Trp Asp Val Val Glu Trp Ser Asp						
			260		265		270
	Asp Gln Ala Val Phe Thr Phe Val Tyr Asp Thr Ile Gln Leu Thr Ile						
25			275		280		285
	Thr Phe Glu Glu Ser Val Val Gly Phe Pro Phe Leu Asp Lys Arg Tyr						
			290		295		300
30	Arg Lys Ile Val Asp Val Asn Phe Gln Ser Leu Leu Asp Glu Asp Gln						
			305		310		315
	Ala Pro Pro Ser Ser Leu Leu Val His Lys Leu Ile Phe Gln Tyr Val						
			325		330		335
35	Glu Glu Lys Glu Ser Trp Lys Lys Thr Cys Thr Thr Gln His Gln Leu						
			340		345		350
	Pro Lys Met Leu Glu Glu Phe Ser Leu Val Val His His Cys Arg Leu						
40			355		360		365
	Leu Gly Glu Glu Ile Glu Tyr Leu Lys Arg Trp Gly Pro Asn Tyr Asn						
			370		375		380
45	Leu Met Asn Ile Asp Ile Asn Asn Asn Glu Leu Arg Leu Leu Phe Ser						
			385		390		395
	Ser Ser Ala Ala Phe Ala Lys Phe Glu Ile Thr Leu Phe Leu Ser Ala						
			405		410		415
50	Tyr Tyr Pro Ser Val Pro Leu Pro Ser Thr Ile Gln Asn His Val Gly						
			420		425		430
	Asn Thr Ser Gln Asp Asp Ile Ala Thr Ile Leu Ser Lys Val Pro Leu						
55			435		440		445

Glu Asn Asn Tyr Leu Lys Asn Val Val Lys Gln Ile Tyr Gln Asp Leu
 450 455 460

5 Phe Gln Asp Cys His Phe Tyr His
 465 470

(2) INFORMATION FOR SEQ ID NO:3:

10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2298 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: cDNA

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CTTTTCTTTG ATTGTCTCTG CTTTAGCGTC TCTAAATCCG GTCACCATGT CGGACCCCGA 60
 AGGCGAGACC TTGCGAAGCA CCTTTCCTC TTATATGGCC GAAGGCGAGC GGCTCTACCT 120
 25 GTGCGGGGAA TTTTCTAAAG CCGCGCAGAG CTTGAGCAAC GCTCTTTACC TTCAGGATGG 180
 AGACAAGAAC TGCCTGGTTG CTCGCTCAAA GTGCTTCCTG AAGATGGGAG ACTTGAGAGAG 240
 30 ATCCCTGAAG GATGCTGARG CTTGCTCCA GAGTGACCCA GCTTTCTGTA AGGGGATTTT 300
 GCAAAAGGCT GAGACACTGT ACACCATGGG AGACTTTGAG TTTGCCTTGG TATTCTATCA 360
 TCGARGCTAC AAGCTGARGC CTGATCGGGA ATTCARARTT GGCATTCAGA AAGCCCAGGA 420
 35 AGCCATCAAC AACTCAGTGG GAAGTCCTTC TTCCATTAAG CTGGAGAACA AAGGGGACCT 480
 CTCCTTCTTA AGCAAGCAGG CTGAGAATAT AAAAGCCCAG CAGAAGCCTC AGCCCATGAA 540
 40 ACACCTCTTA CACCCACCA AGGGAGAGCC CAAGTGGAAG GCCTCGCTCA AGAGTGAGAA 600
 GACTGTCCGC CAGCTTCTGG GGGAGCTCTA CGTGGACAAA GAGTATTTGG AGAAGCTCCT 660
 ATTGGATGAA GACCTGATCA AAGGCACCAT GAAGGGCGGC CTGACTGTGG AGGACCTCAT 720
 45 CATGACGGGC ATCAACTACC TGGATACTCA CAGCAACTTC TGGAGGCAGC AGAAGCCGAT 780
 CTACGCCAGG GAGCGGGACC GGAAGCTGAT GCAAGAGAAA TGGCTGCGGG ACCACAAACG 840
 50 CCGTCCCTCA CAGACAGCCC ATTACATCCT CAAGAGCCTG GAGGACATTG ATATGTTGCT 900
 CACAAGTGGC AGTGCTGAAG GGAGTCTTCA GAAAGCTGAG AAAGTGCTGA AGAAGGTACT 960
 55 GGAATGGAAC AAGGAAGAGG TACCCAACAA GGATGAACTG GTTGGAACCT TGTATAGCTG 1020

CATAGGGAAT GCCCAGATTG AGCTGGGGCA GATGGAGGCA GCCCTGCAGA GCCACAGAAA 1080
 GGACYTGGAG ATCGCCAAGG AATATGACCT TCCTGATGCA AAATCGAGAG CCCTTGACAA 1140
 5 CATTGGCAGA GTTTTGTGCCA GAGTTGGGAA ATTCCAGCAA GCCATTGACA CGTGGGAAGA 1200
 AAAGATCCCT CTGGCAAAAA CCACCCTGGA GAAGACCTGG CTGTTCCACG AGATCGGCCG 1260
 10 CTGCTACTTG GAGCTGGACC AGGCCTGGCA GGCCAGAAAT TATGGCGAGA AGTCCCAGCA 1320
 GTGTGCCGAG GAGGAAGGGG ACATTGAGTG GCAACTGAAT GCCAGTGTTC TGGTGGCCCA 1380
 GGCACAAGTG AAGCTGAGAG ACTTCGAGTC AGCCGTGAAC AATTTTGAGA AGGCCCTGGA 1440
 15 GAGAGCAAAG CTTGTGCATA ACAACGAGGC GCAGCAGGCC ATCATCAGTG CCTTGGACGA 1500
 TGCCAACAAG GGTATCATCA GAGAACTGAG GAAAACCAAC TACGTGGAGA ATCTCAAAGA 1560
 AAAAAGCGAG GGAGAAGCTT CACTGTATGA AGATAGAATA ATAACAAGAG AGAAGGACAT 1620
 20 GAGGAGAGTG AGAGATGAGC CCGAGAAGGT GGTGAAGCAG TGGGACCATA GTGAGGATGA 1680
 GAAAGAGACA GATGAGGACG ATGAGGCTTT TGGGGAAGCT CTGCAGAGCC CAGCAAGCGG 1740
 25 AAAGCAGAGT GTGGAAGCAG GAAAAGCCAG AAGCGATTTG GGAGCAGTTG CCAAGGGCCT 1800
 GTCAGGAGAA TTAGGCACAA GATCAGGAGA AACAGGCAGG AAGCTACTAG AAGCTGGCAG 1860
 AAGAGAGTCA AGAGAAATTT ATAGGAGGCC TTCGGGAGAA TTAGAGCAAA GACTCTCAGG 1920
 30 AGAATTCAGC AGACAGGAAC CAGAAGAACT AAAGAACTTT TCAGAAGTGG GCAGAAGAGA 1980
 SCCAGAAGAA YTGGGAAAAA CACAATTTGG AGAAATAGGA GAAACGAAAA AAACAGGAAA 2040
 35 TGAGATGGAA AAGGAATATG AATGAAGCCA TCGGTAGAGA TGAGGATCAG GAAGCTGGTG 2100
 TTCAGAGGGA TCATGGGATT TTATTAAACT GGATTTTCAA GCGATTTGTC TGTATAGGA 2160
 AAAATGAGGG TTTTACTTYT GCTGCTTTCC ATCACTATTT TGCCATTAAA TAGGTGTCTT 2220
 40 TCACTCTTGC MAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 2280
 AAAAAAAAAA AAAAAAAA 2298

45 (2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 672 amino acids
 (B) TYPE: amino acid
 50 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

55

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

5	Met	Ser	Asp	Pro	Glu	Gly	Glu	Thr	Leu	Arg	Ser	Thr	Phe	Pro	Ser	Tyr	1	5	10	15
	Met	Ala	Glu	Gly	Glu	Arg	Leu	Tyr	Leu	Cys	Gly	Glu	Phe	Ser	Lys	Ala	20	25	30	
10	Ala	Gln	Ser	Phe	Ser	Asn	Ala	Leu	Tyr	Leu	Gln	Asp	Gly	Asp	Lys	Asn	35	40	45	
	Cys	Leu	Val	Ala	Arg	Ser	Lys	Cys	Phe	Leu	Lys	Met	Gly	Asp	Leu	Glu	50	55	60	
15	Arg	Ser	Leu	Lys	Asp	Ala	Glu	Ala	Ser	Leu	Gln	Ser	Asp	Pro	Ala	Phe	65	70	75	80
	Cys	Lys	Gly	Ile	Leu	Gln	Lys	Ala	Glu	Thr	Leu	Tyr	Thr	Met	Gly	Asp	85	90	95	
20	Phe	Glu	Phe	Ala	Leu	Val	Phe	Tyr	His	Arg	Xaa	Tyr	Lys	Leu	Xaa	Pro	100	105	110	
	Asp	Arg	Glu	Phe	Xaa	Xaa	Gly	Ile	Gln	Lys	Ala	Gln	Glu	Ala	Ile	Asn	115	120	125	
25	Asn	Ser	Val	Gly	Ser	Pro	Ser	Ser	Ile	Lys	Leu	Glu	Asn	Lys	Gly	Asp	130	135	140	
30	Leu	Ser	Phe	Leu	Ser	Lys	Gln	Ala	Glu	Asn	Ile	Lys	Ala	Gln	Gln	Lys	145	150	155	160
	Pro	Gln	Pro	Met	Lys	His	Leu	Leu	His	Pro	Thr	Lys	Gly	Glu	Pro	Lys	165	170	175	
35	Trp	Lys	Ala	Ser	Leu	Lys	Ser	Glu	Lys	Thr	Val	Arg	Gln	Leu	Leu	Gly	180	185	190	
40	Glu	Leu	Tyr	Val	Asp	Lys	Glu	Tyr	Leu	Glu	Lys	Leu	Leu	Leu	Asp	Glu	195	200	205	
	Asp	Leu	Ile	Lys	Gly	Thr	Met	Lys	Gly	Gly	Leu	Thr	Val	Glu	Asp	Leu	210	215	220	
45	Ile	Met	Thr	Gly	Ile	Asn	Tyr	Leu	Asp	Thr	His	Ser	Asn	Phe	Trp	Arg	225	230	235	240
	Gln	Gln	Lys	Pro	Ile	Tyr	Ala	Arg	Glu	Arg	Asp	Arg	Lys	Leu	Met	Gln	245	250	255	
50	Glu	Lys	Trp	Leu	Arg	Asp	His	Lys	Arg	Arg	Pro	Ser	Gln	Thr	Ala	His	260	265	270	
55	Tyr	Ile	Leu	Lys	Ser	Leu	Glu	Asp	Ile	Asp	Met	Leu	Leu	Thr	Ser	Gly				

	275	280	285
5	Ser Ala Glu Gly Ser Leu Gln Lys Ala Glu Lys Val Leu Lys Lys Val 290 295 300		
	Leu Glu Trp Asn Lys Glu Glu Val Pro Asn Lys Asp Glu Leu Val Gly 305 310 315 320		
10	Asn Leu Tyr Ser Cys Ile Gly Asn Ala Gln Ile Glu Leu Gly Gln Met 325 330 335		
	Glu Ala Ala Leu Gln Ser His Arg Lys Asp Leu Glu Ile Ala Lys Glu 340 345 350		
15	Tyr Asp Leu Pro Asp Ala Lys Ser Arg Ala Leu Asp Asn Ile Gly Arg 355 360 365		
	Val Phe Ala Arg Val Gly Lys Phe Gln Gln Ala Ile Asp Thr Trp Glu 370 375 380		
20	Glu Lys Ile Pro Leu Ala Lys Thr Thr Leu Glu Lys Thr Trp Leu Phe 385 390 395 400		
	His Glu Ile Gly Arg Cys Tyr Leu Glu Leu Asp Gln Ala Trp Gln Ala 405 410 415		
25	Gln Asn Tyr Gly Glu Lys Ser Gln Gln Cys Ala Glu Glu Glu Gly Asp 420 425 430		
	Ile Glu Trp Gln Leu Asn Ala Ser Val Leu Val Ala Gln Ala Gln Val 435 440 445		
	Lys Leu Arg Asp Phe Glu Ser Ala Val Asn Asn Phe Glu Lys Ala Leu 450 455 460		
35	Glu Arg Ala Lys Leu Val His Asn Asn Glu Ala Gln Gln Ala Ile Ile 465 470 475 480		
	Ser Ala Leu Asp Asp Ala Asn Lys Gly Ile Ile Arg Glu Leu Arg Lys 485 490 495		
40	Thr Asn Tyr Val Glu Asn Leu Lys Glu Lys Ser Glu Gly Glu Ala Ser 500 505 510		
	Leu Tyr Glu Asp Arg Ile Ile Thr Arg Glu Lys Asp Met Arg Arg Val 515 520 525		
	Arg Asp Glu Pro Glu Lys Val Val Lys Gln Trp Asp His Ser Glu Asp 530 535 540		
50	Glu Lys Glu Thr Asp Glu Asp Asp Glu Ala Phe Gly Glu Ala Leu Gln 545 550 555 560		
	Ser Pro Ala Ser Gly Lys Gln Ser Val Glu Ala Gly Lys Ala Arg Ser 565 570 575		

Asp Leu Gly Ala Val Ala Lys Gly Leu Ser Gly Glu Leu Gly Thr Arg
 580 585 590
 Ser Gly Glu Thr Gly Arg Lys Leu Leu Glu Ala Gly Arg Arg Glu Ser
 5 595 600 605
 Arg Glu Ile Tyr Arg Arg Pro Ser Gly Glu Leu Glu Gln Arg Leu Ser
 610 615 620
 Gly Glu Phe Ser Arg Gln Glu Pro Glu Glu Leu Lys Lys Leu Ser Glu
 10 625 630 635 640
 Val Gly Arg Arg Xaa Pro Glu Glu Leu Gly Lys Thr Gln Phe Gly Glu
 645 650 655
 15 Ile Gly Glu Thr Lys Lys Thr Gly Asn Glu Met Glu Lys Glu Tyr Glu
 660 665 670

20 (2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1010 base pairs
 (B) TYPE: nucleic acid
 25 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

35 GGAAGAGCCA CCATCCCTGC CCCCGTTTTT CCACCGGGGA GTCTGTACAG AGATTTTCTT 60
 ACGTTTTTAT TTTTGCCTC AGAGGGATGG GATTGGGGAG GAGGGGATGG GCAGCGGAGG 120
 GTTGGGGGCA TGGTCTGCAG GCTCATCTGT GTCCGCCTTT CACTCCACTA ATGCTGTCTC 180
 40 AGTGTTTTCT CTCTCTCTCT TTCGAGCTTG CACTCCGGTA CCCGACCCGG CGCCCTGGCC 240
 CATCCCATGC CGGGGGGCCA GTGGAAAGAA GACAGGCCGT CCAGCCCGTG CCCGCCTGCG 300
 45 GCGGGGGCAC CCAGCAAGCC CGCCCACCGC CCGCTGCCTC ACCTGCTTCG CCACAGACTC 360
 TTGTTCCCAG CCCCTTGGGG CCTCCGTGTT TGGGGTGGGG GAGCTGCTTA GAGACTGTGC 420
 CCGTCCTCGG CCCCCACCC TGAAGTGCCA GCACCACCAG CACCAGATCT TCCGCCGCCA 480
 50 CACCGCATTG AGGACACGCC GGCCGGGCCG CTTCGTCTCA AGTTGTATAA AGTTGTCTCC 540
 GTGTCCCCTC CTCCCTCTGC CCCAGTGTG TCTTCTGATT TTTTTTCCC CTTTCCCTCC 600
 55 CTCCCTCTCC GCATTCTTCC CTTGGTTCAG CACAGGTAAA ACGGTTCCCC TCCCTCCCTG 660

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CCTTCATGGA TCACCAGCTC ACGTCATGTT GCCTTCTCTT TTCTTTGTGT GTGTGTTTAT      720
TTAAGTTATT TTTCTTCCTC CTCTCCCTTT TCTTTTTTGGC CCTCCCTCCC TCCCTCTTCT      780
5  GCCATGTAAC TGGAGGATGT GCTATGAGTT TGCAAACAGC TGGACTGTCA GGCTGCTTTT      840
TTTTCCAGAT GTTCTTCTTC TGCTTCCCCT TCCCCTCCTC TCCCCTCCTT TTCCTTCCTT      900
10 CCTTCCTTTC CTTGGAGCAC TGAGCACCAT TTGGAAGCTT GAGAGAAACC AAAATTAAAG      960
AGAGAAAGAG AGAGCGTGCA CGCTCCTGCT TTGTCAAAAA AAAAAAAAAA      1010

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(2) INFORMATION FOR SEQ ID NO:6:

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15  (i) SEQUENCE CHARACTERISTICS:
      (A) LENGTH: 205 amino acids
      (B) TYPE: amino acid
      (C) STRANDEDNESS:
      (D) TOPOLOGY: linear

20  (ii) MOLECULE TYPE: protein

25  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Gly Ser Gly Gly Leu Gly Ala Trp Ser Ala Gly Ser Ser Val Ser
1          5          10          15
30  Ala Phe His Ser Thr Asn Ala Val Ser Val Phe Ser Leu Ser Leu Phe
      20          25          30
35  Arg Ala Cys Thr Pro Val Pro Asp Pro Ala Pro Trp Pro Ile Pro Cys
      35          40          45
      Arg Gly Ala Ser Gly Lys Lys Thr Gly Arg Pro Ala Arg Ala Arg Leu
      50          55          60
40  Arg Arg Gly His Pro Ala Ser Pro Pro Thr Ala Arg Cys Leu Thr Cys
      65          70          75          80
      Phe Ala Thr Asp Ser Cys Ser Gln Pro Leu Gly Ala Ser Val Phe Gly
      85          90          95
45  Val Gly Glu Leu Leu Arg Asp Cys Ala Arg Pro Arg Pro Pro Thr Leu
      100          105          110
50  Lys Cys Gln His His Gln His Gln Ile Phe Arg Arg His Thr Ala Leu
      115          120          125
      Arg Thr Arg Arg Pro Gly Arg Phe Val Ser Ser Cys Ile Lys Leu Ser
      130          135          140
55  Pro Cys Pro Leu Leu Pro Leu Pro Pro Val Phe Leu Leu Ile Phe Phe

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	145		150		155		160									
	Ser	Pro	Phe	Pro	Pro	Ser	Leu	Ser	Ala	Phe	Phe	Pro	Trp	Phe	Ser	Thr
					165					170					175	
5	Gly	Lys	Thr	Val	Pro	Leu	Pro	Pro	Cys	Leu	His	Gly	Ser	Pro	Ala	His
				180					185					190		
10	Val	Met	Leu	Pro	Ser	Leu	Phe	Phe	Val	Cys	Val	Phe	Ile			
			195					200					205			

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

15 (A) LENGTH: 2409 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: cDNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

	ATTTYGCTCA	TCAACCTCAT	TATAGAACAT	ATGATTTGTG	ATACAGATCC	TGAACTTGGA	60
	GGAGCAGTCC	AGCTTATGGG	CCTGCTTCGA	ACTTTAGTTG	ACCCAGAGAA	CATGCTAGCC	120
30	ACTGCCMATA	AAACASAAAA	GACTGAATTT	CTGGGTTTCT	TCTACAAGCA	CTGTATGCAT	180
	GTTCTCWCTG	CTCCTTTACT	AGCAAATACA	ACAGAAGACA	AACCTAGTAA	AGATGATTTT	240
35	CAGACTGCCC	AACATATTGG	ACTTGATTTG	GAATTGTTAA	CATTTTGTGT	GGAGCACCAT	300
	ACCTACCACA	TAAAGAACTA	CATTATTAAT	AAGGATATCC	TCCGGAGAGT	GCTAGTTCTT	360
	ATGGCCTCGA	AGCATGCTTT	CTTGGCATT	TGTGCCCTTC	GTTTTAAAAG	AAAGATTATT	420
40	GGATTAAAAG	ATGAGTTTTA	CAACCGCTAC	ATAATGAAAA	GTTTTTTGTT	TGAACCAGTA	480
	GTGAAAGCAT	TTCTCAACAA	TGGATCCCGC	TACAATCTGA	TGAACTCTGC	CATAATAGAG	540
45	ATGTTTGAAT	TTATTAGAGT	GGAAGATATA	AAATCATTAA	CTGCTCATGT	AATTGAAAAT	600
	TACTGGAAAAG	CACTGGAAGA	TGTAGATTAT	GTACAGACAT	TTAAAGGATT	AAAAGTGAAG	660
	TTTGAACAAC	AAAGAGAAAAG	GCAAGATAAT	CCCAAACTTG	ACAGTATGCG	TTCCATTTTG	720
50	AGGAATCACA	GATATCGAAG	AGATGCCAGA	ACACTAGAAG	ATGAAGAAGA	GATGTGGTTT	780
	AACACAGATG	AAGATGACAT	GGAAGATGGA	GAAGCTGTAG	TGTCTCCATC	TGACAAAAC	840
55	AAAAATGATG	ATGATATTAT	GGATCCAATA	AGTAAATTCA	TGGAAAGGAA	GAAATTAAAA	900

GAAAGTGAGG AAAAGGAAGT GCTTCTGAAA ACAAACCTTT CTGGACGGCA GAGCCCAAGT 960
TTCAAGCTTT CCCTGTCCAG TGGAACGAAG ACTAACCTCA CCAGCCAGTC ATCTACAACA 1020
5 AATCTGCCTG GTTCTCCGGG ATCACCTGGA TCCCCAGGAT CTCCAGGCTC TCCTGGATCC 1080
GTACCTAAAA ATACATCTCA GACGGCAGCT ATTACTACAA AGGGAGGCCT CGTGGGTCTG 1140
GTAGATTATC CTGATGATGA TGAAGATGAT GATGAGGATG AAGATAAGGA AGATACGTTA 1200
10 CCATTGTCAA AGAAAGCAAA ATTTGATTCA TAATAATGGC AACGGCCTAG GATCAGTACC 1260
TGTTGAAAAA AACTGGTTCT CCACCCCTCC CCCATACAAA ATCCACAAAA AAGCGCAGTG 1320
GTCTCTTGTG AATGACTGAC ACAGATCAGC CTCTTACACT TGA CTCTCTGC TCATCAAGTG 1380
CCAATTCAAT GGAGCAGGAG GAGGGGATAT CATATATTTA GGGGAAAGAC TTAAGCCTTT 1440
GAGCTCTCCA GCTTGGACCA CACATTGCCC TTTTCTCAGG GAAGGAAATG GAAACAAAAA 1500
20 GCCAACAGGG CAGGGGTTTT GTAAGTGGA CTCTGGATTG ACTGGTCAGT TGCTACAATC 1560
AGAATATGCT TTCTTGGACC ATGTTTGAGA CTCAGAAGAA TGGCCTTTCT GCCATAATTC 1620
25 TTCACTAGTC AAGAATGCCA GCAGTTTCTT TGTATAAAGA GACCTGCCTT TAAAATCATA 1680
CATCTGAAC ATTTTAGTCA AGCTACAACA GGT TTGGAAA ACCTCTGTGG GGGAGGGGCG 1740
AGTATAAAGT TTTCTCTTT TTTAACTGTT CCCTTTGCCC TTCAAAGTGC AGATATTTTT 1800
30 TTTT TTAAGT GGGGACTTCT CCCTACTTGA TTAAAGATTG AGTGGAATTC TAGATGTGGT 1860
CATTTGTGTC ATAATTTTTT TGTTTTATTT TGTTTTTGAT TTTTTTTTTT CTCCCCTGAG 1920
35 TGTATGCTTA GTTGTGAGT ATATATATTT GGGACCATTA AACTTTTTTT TGATGTAATA 1980
TAACCTAACG TTGTGCTGGT ACCTGTTTTA CCATGTGTAA TTTTGTCT ACATCACAGT 2040
TCTTAATTIG TTTAGAGTTT TATGAAAGAT GGTATAGTTT TTATTGACAA AAGCAAAGTA 2100
40 ATCTTACAAC TATGTGCATA CAAAAGCAAT ACTATTTTGT GACTAAATAT TTTATATTAA 2160
AATTTACATC AGCAACTGTC TTGAGAATTC AGGGAAATAG AATGGAATTT AAAACTTCAA 2220
45 CAGTTTTGTT AAATCTAGAA ACATGAAATT RGTATTCCAA AGAGATTCTG AAATTTCTTT 2280
TCTKGGGGAA ATGACGGTAC ATTAAATCAA AATTGRGGAT GGATGATTTA AAAACATTTG 2340
ACTTTTTAAT AATAAAAAGA AAAGTGAAGA GTAAGAGAAA TTGTAAAAAA AAAAAAAAAA 2400
50 AAAAAAAAAA 2409

(2) INFORMATION FOR SEQ ID NO:8:

55 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 400 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: protein

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Ile Cys Asp Thr Asp Pro Glu Leu Gly Gly Ala Val Gln Leu Met
 1 5 10 15

Gly Leu Leu Arg Thr Leu Val Asp Pro Glu Asn Met Leu Ala Thr Ala
 20 25 30

Xaa Lys Thr Xaa Lys Thr Glu Phe Leu Gly Phe Phe Tyr Lys His Cys
 35 40 45

Met His Val Leu Xaa Ala Pro Leu Leu Ala Asn Thr Thr Glu Asp Lys
 50 55 60

Pro Ser Lys Asp Asp Phe Gln Thr Ala Gln Leu Leu Ala Leu Val Leu
 65 70 75 80

Glu Leu Leu Thr Phe Cys Val Glu His His Thr Tyr His Ile Lys Asn
 85 90 95

Tyr Ile Ile Asn Lys Asp Ile Leu Arg Arg Val Leu Val Leu Met Ala
 100 105 110

Ser Lys His Ala Phe Leu Ala Leu Cys Ala Leu Arg Phe Lys Arg Lys
 115 120 125

Ile Ile Gly Leu Lys Asp Glu Phe Tyr Asn Arg Tyr Ile Met Lys Ser
 130 135 140

Phe Leu Phe Glu Pro Val Val Lys Ala Phe Leu Asn Asn Gly Ser Arg
 145 150 155 160

Tyr Asn Leu Met Asn Ser Ala Ile Ile Glu Met Phe Glu Phe Ile Arg
 165 170 175

Val Glu Asp Ile Lys Ser Leu Thr Ala His Val Ile Glu Asn Tyr Trp
 180 185 190

Lys Ala Leu Glu Asp Val Asp Tyr Val Gln Thr Phe Lys Gly Leu Lys
 195 200 205

Leu Arg Phe Glu Gln Gln Arg Glu Arg Gln Asp Asn Pro Lys Leu Asp
 210 215 220

Ser Met Arg Ser Ile Leu Arg Asn His Arg Tyr Arg Arg Asp Ala Arg

	225		230		235		240									
	Thr	Leu	Glu	Asp	Glu	Glu	Glu	Met	Trp	Phe	Asn	Thr	Asp	Glu	Asp	Asp
					245					250					255	
5	Met	Glu	Asp	Gly	Glu	Ala	Val	Val	Ser	Pro	Ser	Asp	Lys	Thr	Lys	Asn
				260					265						270	
10	Asp	Asp	Asp	Ile	Met	Asp	Pro	Ile	Ser	Lys	Phe	Met	Glu	Arg	Lys	Lys
			275					280					285			
	Leu	Lys	Glu	Ser	Glu	Glu	Lys	Glu	Val	Leu	Leu	Lys	Thr	Asn	Leu	Ser
	290						295					300				
15	Gly	Arg	Gln	Ser	Pro	Ser	Phe	Lys	Leu	Ser	Leu	Ser	Ser	Gly	Thr	Lys
	305				310						315					320
	Thr	Asn	Leu	Thr	Ser	Gln	Ser	Ser	Thr	Thr	Asn	Leu	Pro	Gly	Ser	Pro
					325					330					335	
20	Gly	Ser	Pro	Gly	Ser	Pro	Gly	Ser	Pro	Gly	Ser	Pro	Gly	Ser	Val	Pro
				340				345					350			
25	Lys	Asn	Thr	Ser	Gln	Thr	Ala	Ala	Ile	Thr	Thr	Lys	Gly	Gly	Leu	Val
			355				360						365			
	Gly	Leu	Val	Asp	Tyr	Pro	Asp	Asp	Asp	Glu	Asp	Asp	Asp	Glu	Asp	Glu
	370						375					380				
30	Asp	Lys	Glu	Asp	Thr	Leu	Pro	Leu	Ser	Lys	Lys	Ala	Lys	Phe	Asp	Ser
	385				390						395					400

(2) INFORMATION FOR SEQ ID NO:9:

35

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 951 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

40

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

45

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

50	GCCAGGCAGG GTGTGGGGGC AGCTGTGCCA ATCTACCTCA CAGGCCACC CCCTGCCGGG	60
	CATGCCGTGG GATCATGGGC AGGGAAGGCT CTGGGGGTCG GAGACACCGC TGCTTAGCAC	120
	CCCCAGCCAG AACACCCTGA GGGTCTCGGG GCTCTGGAGA GAGTGGGGCG GGAGGAAGAA	180
55	TTGGCACCTT CCTAGGGAAG GAGACGAGCG CTTGCCTTG ATTCTCCGAG AAGCCTCCGA	240

GAAGTGCTTT AAGTGTGTTT GCATGCSCCA GGCGGTGGGC AGCGGGGGCC TGTCCARCCC 300
 TCTCCCGCCA TCCTTCCCCA AGTGACGTCC ACTGCCTTGT CACCAGCGAC CTGCCTGTCA 360
 5 TGCCCAACCC CTGAGGAAGC ATGGGGACCC TAACACCCTG GTGCCCTGCA CCAGACAGGC 420
 CGTGGTCAGG CCCAGGCCAC CGGCCGGGTT CTGCCACARC TTCCCACGTG CTTGCTGACA 480
 TGCSTGTGCC TGTGTGTGGT GTCTGTTGCT GTGTCGTGAA ACTGTGACCA TCACTCAGTC 540
 10 CAAACAAGTG AGTGGCCCTS GAGGCCACAG TTATGCAACT TTCAGTGTGT GTCATAACGA 600
 CGTCACTGCT TTTTAAACTC GATAACTCTT TATTTTAGTA AAATGCCCAG GAGTCCTGGA 660
 15 AGCTACGCGG ACTTGCAGAG GTTTTATTTT TTGGCCTTAG AATCTGCAGA AATTAGGAGG 720
 CACCGAGCCC AGCGCAGCAG CCTCGGACCC GGATTGCGTT TGCCTTAGCG GATATGTTTA 780
 TACAGATGAA TATAAAATGT TTTTTCTTTT GGGCTTTTTG CTTCTTTTTT CCCCCCTTC 840
 20 TCACCTTCCC TTCTCCCTGA CCCCAACCCC CAAAAAGCT ACTTCTTCAT TCCGTGGTAC 900
 GATTATTTTT TTTAACTAAA GGAAGATAAA ATTCTAAAAA AAAAAAAAAA A 951

25 (2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 87 amino acids
 (B) TYPE: amino acid
 30 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

40 Met Pro Trp Asp His Gly Gln Gly Arg Leu Trp Gly Ser Glu Thr Pro
 1 5 10 15
 Leu Leu Ser Thr Pro Ser Gln Asn Thr Leu Arg Val Ser Gly Leu Trp
 20 25 30
 45 Arg Glu Trp Gly Gly Arg Lys Asn Trp His Leu Pro Arg Glu Gly Asp
 35 40 45
 Glu Arg Phe Ala Leu Ile Leu Arg Glu Ala Ser Glu Lys Cys Phe Lys
 50 50 55 60
 Cys Val Cys Met Xaa Gln Ala Val Gly Ser Gly Gly Leu Ser Xaa Pro
 65 70 75 80
 55 Leu Pro Pro Ser Phe Pro Lys

85

(2) INFORMATION FOR SEQ ID NO:11:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1899 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: cDNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGCCGCTTGT GTCCACGGGA CGCGGGCGGA TCTTCTCCGG CCATGAGGAA GCCAGCCGCT 60
 20 GGCTTCCTTC CCTCACTCCT GAAGGTGCTG CTCCTGCCTC TGGCACCTGC CGCAGCCCAG 120
 GATTCGACTC AGGCCTCCAC TCCAGGCAGC CCTCTCTCTC CTACCGAATA CGAACGCTTC 180
 25 TTGCGACTGC TGA CTCCAAC CTGGAAGGCA GAGACTACCT GCCGTCTCCG TGCAACCCAC 240
 GGCTGCCGGA ATCCCACACT CGTCCAGCTG GACCAATATG AAAACCACGG CTTAGTGCCC 300
 GATGGTGCTG TCTGCTCCAA CCTCCCTTAT GCCTCCTGGT TTGAGTCTTT CTGCCAGTTC 360
 30 ACTCACTACC GTTGCTCCAA CCACGTCTAC TATGCCAAGA GAGTCCTGTG TTCCCAGCCA 420
 GTCTCTATTC TCTCACCTAA CACTCTCAAG GAGATAGAAG CTTCAGCTGA AGTCTCACCC 480
 ACCACGATGA CCTCCCCCAT CTCACCCAC TTCACAGTGA CAGAACGCCA GACCTTCCAG 540
 35 CCCTGGCCTG AGAGGCTCAG CAACAACGTG GAAGAGCTCC TACAATCCTC CTTGTCCCTG 600
 GGAGGCCAGG AGCAAGCGCC AGAGCACAAG CAGGAGCAAG GAGTGGAGCA CAGGCAGGAG 660
 40 CCGACACAAG AACACAAGCA GGAAGAGGGG CAGAAACAGG AAGAGCAAGA AGAGGAACAG 720
 GAAGAGGAGG GAAAGCAGGA AGAAGGACAG GGGACTAAGG AGGGACGGGA GGCTGTGTCT 780
 CAGCTGCAGA CAGACTCAGA GCCCAAGTTT CACTCTGAAT CTCTATCTTC TAACCCCTTC 840
 45 TCTTTTGCTC CCCGGGTACG AGAAGTAGAG TCTACTCTTA TGATAATGGA GAACATCCAG 900
 GAGCTCATTC GATCAGCCCA GGAAATAGAT GAAATGAATG AAATATATGA TGAGAACTCC 960
 50 TACTGGAGAA ACCAAAACCC TGGCAGCCTC CTGCAGCTGC CCCACACAGA GGCCTTGCTG 1020
 GTGCTGTGCT ATTCGATCGT GGAGAATACC TGCATCATAA CCCCCACAGC CAAGGCCTGG 1080
 AAGTACATGG AGGAGGAGAT CTTGGTTTC GGGAAGTCGG TCTGTGACAG CCTTGGGCGG 1140
 55

CGACACATGT CTACCTGTGC CCTCTGTGAC TTCTGCTCCT TGAAGCTGGA GCAGTGCCAC 1200
 TCAGAGGCCA GCCTGCAGCG GCAACAATGC GACACCTCCC ACAAGACTCC CTTTGTGAGC 1260
 5 CCCTTGCTTG CCTCCAGAG CCTGTCCATC GGCAACCAGG TAGGGTCCCC AGAATCAGGC 1320
 CGCTTTTACG GGCTGGATTT GTACGGTGGG CTCCACATGG ACTTCTGGTG TGCCCGGCTT 1380
 10 GCCACGAAAG GCTGTGAAGA TGTCCGAGTC TCTGGGTGGC TCCAGACTGA GTTCCTTAGC 1440
 TTCCAGGATG GGGATTTCCC TACCAAGATT TGTGACACAG ACTATATCCA GTACCCAAAC 1500
 TACTGTTCTT TCAAAAGCCA GCAGTGTCTG ATGAGAAACC GCAATCGGAA GGTGTCCCGC 1560
 15 ATGAGATGTC TGCAGAATGA GACTTACAGT GCGCTGAGCC TGGCAAAAGT GAGGACGTTG 1620
 TGCTTTTCGAT GGAGCCAGGA GTTCAGCACC TTGACTCTAG GCCAGTTCGG ATGAGCTKGS 1680
 GTTTATTTTG CCCACACCCC AGCCCAACCT GCCCASGTTT TCTATTGTTT TGAGACCCCA 1740
 20 TTGCTTTCAG GCTGCCCCTT CTGGGTCTGT TACTCGGCCC CTAMTCACAT TTCCTTGGGT 1800
 TGGAGCAACA GTCCCAGAGA GGGCCACGGT GGGAGCTGCG CCCTCCTTAA AAGATGACTT 1860
 25 TACATAAAAT GTTGATCTTC AAAAAAAAAA AAAAAAAAAA 1899

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
 30 (A) LENGTH: 543 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: protein

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu
 1 5 10 15
 45 Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser
 20 25 30
 Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Glu Arg Phe Phe Ala
 35 40 45
 50 Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala
 50 55 60
 55 Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu
 65 70 75 80

	Asn	His	Gly	Leu	Val	Pro	Asp	Gly	Ala	Val	Cys	Ser	Asn	Leu	Pro	Tyr	
					85					90					95		
5	Ala	Ser	Trp	Phe	Glu	Ser	Phe	Cys	Gln	Phe	Thr	His	Tyr	Arg	Cys	Ser	
				100					105					110			
	Asn	His	Val	Tyr	Tyr	Ala	Lys	Arg	Val	Leu	Cys	Ser	Gln	Pro	Val	Ser	
			115					120					125				
10	Ile	Leu	Ser	Pro	Asn	Thr	Leu	Lys	Glu	Ile	Glu	Ala	Ser	Ala	Glu	Val	
		130					135					140					
	Ser	Pro	Thr	Thr	Met	Thr	Ser	Pro	Ile	Ser	Pro	His	Phe	Thr	Val	Thr	
	145					150					155					160	
15	Glu	Arg	Gln	Thr	Phe	Gln	Pro	Trp	Pro	Glu	Arg	Leu	Ser	Asn	Asn	Val	
					165					170					175		
	Glu	Glu	Leu	Leu	Gln	Ser	Ser	Leu	Ser	Leu	Gly	Gly	Gln	Glu	Gln	Ala	
20					180					185				190			
	Pro	Glu	His	Lys	Gln	Glu	Gln	Gly	Val	Glu	His	Arg	Gln	Glu	Pro	Thr	
			195					200					205				
25	Gln	Glu	His	Lys	Gln	Glu	Glu	Gly	Gln	Lys	Gln	Glu	Glu	Gln	Glu	Glu	
		210					215					220					
	Glu	Gln	Glu	Glu	Glu	Gly	Lys	Gln	Glu	Glu	Gly	Gln	Gly	Thr	Lys	Glu	
	225					230					235					240	
30	Gly	Arg	Glu	Ala	Val	Ser	Gln	Leu	Gln	Thr	Asp	Ser	Glu	Pro	Lys	Phe	
					245					250					255		
	His	Ser	Glu	Ser	Leu	Ser	Ser	Asn	Pro	Ser	Ser	Phe	Ala	Pro	Arg	Val	
35					260				265					270			
	Arg	Glu	Val	Glu	Ser	Thr	Pro	Met	Ile	Met	Glu	Asn	Ile	Gln	Glu	Leu	
			275					280					285				
40	Ile	Arg	Ser	Ala	Gln	Glu	Ile	Asp	Glu	Met	Asn	Glu	Ile	Tyr	Asp	Glu	
		290					295					300					
	Asn	Ser	Tyr	Trp	Arg	Asn	Gln	Asn	Pro	Gly	Ser	Leu	Leu	Gln	Leu	Pro	
	305					310					315					320	
45	His	Thr	Glu	Ala	Leu	Leu	Val	Leu	Cys	Tyr	Ser	Ile	Val	Glu	Asn	Thr	
					325					330					335		
	Cys	Ile	Ile	Thr	Pro	Thr	Ala	Lys	Ala	Trp	Lys	Tyr	Met	Glu	Glu	Glu	
50					340				345					350			
	Ile	Leu	Gly	Phe	Gly	Lys	Ser	Val	Cys	Asp	Ser	Leu	Gly	Arg	Arg	His	
			355					360					365				
55	Met	Ser	Thr	Cys	Ala	Leu	Cys	Asp	Phe	Cys	Ser	Leu	Lys	Leu	Glu	Gln	

	370		375		380
	Cys His Ser Glu Ala Ser Leu Gln Arg Gln Gln Cys Asp Thr Ser His				
	385		390		395 400
5	Lys Thr Pro Phe Val Ser Pro Leu Leu Ala Ser Gln Ser Leu Ser Ile				
		405		410	415
10	Gly Asn Gln Val Gly Ser Pro Glu Ser Gly Arg Phe Tyr Gly Leu Asp				
		420		425	430
	Leu Tyr Gly Gly Leu His Met Asp Phe Trp Cys Ala Arg Leu Ala Thr				
		435		440	445
15	Lys Gly Cys Glu Asp Val Arg Val Ser Gly Trp Leu Gln Thr Glu Phe				
		450		455	460
	Leu Ser Phe Gln Asp Gly Asp Phe Pro Thr Lys Ile Cys Asp Thr Asp				
		465		470	475 480
20	Tyr Ile Gln Tyr Pro Asn Tyr Cys Ser Phe Lys Ser Gln Gln Cys Leu				
		485		490	495
	Met Arg Asn Arg Asn Arg Lys Val Ser Arg Met Arg Cys Leu Gln Asn				
25		500		505	510
	Glu Thr Tyr Ser Ala Leu Ser Leu Ala Lys Val Arg Thr Leu Cys Phe				
		515		520	525
30	Arg Trp Ser Gln Glu Phe Ser Thr Leu Thr Leu Gly Gln Phe Gly				
		530		535	540

(2) INFORMATION FOR SEQ ID NO:13:

35 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 722 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

40 (ii) MOLECULE TYPE: cDNA

45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

	CGACCTTCCC AGCAATATGC ATCTTGCACG TCTGGTCGGC TCCTGCTCCC TCCTTCTGCT	60
50	ACTGGGGGCC CTGTCTGGAT GGGCGGCCAG CGATGACCCC ATTGAGAAGG TCATTGAAGG	120
	GATCAACCGA GGGCTGAGCA ATGCAGAGAG AGAGGTGGGC AAGGCCCTGG ATGGCATCAA	180
55	CAGTGAATC ACGCATGCCG GAAGGGAAGT GGAGAAGGTT TTCAACGGAC TTAGCAACAT	240

GGGGAGCCAC ACCGGCAAGG AGTTGGACAA AGGCGTCCAG GGGCTCAACC ACGGCATGGA 300
 CAAGGTTGCC CATGAGATCA ACCATGGTAT TGGACAAGCA GGAAAGGAAG CAGAGAAGCT 360
 5 TGGCCATGGG GTCAACAACG CTGCTGGACA GGGCAACCAT CAAAGCGGAT CTTCCAGCCA 420
 TCAAGGAGGG GCCACAACCA CGCCGTTAGC CTCTGGGGCC TCGGTCAACA CGCCTTTCAT 480
 CAACCTTCCC GCCCTGTGGA GGAGCGTCGC CAACATCATG CCCTAAACTG GCATCCGGCC 540
 10 TTGCTGGGAG AATAATGTCG CCGTTGTCAC ATCAGCTGAC ATGACCTGGA GGGGTTGGGG 600
 GTGGGGGACA GGTTTCTGAA ATCCCTGAAG GGGGTTGTAC TGGGATTTGT GAATAAACTT 660
 15 GATACACTAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 720
 AA 722

(2) INFORMATION FOR SEQ ID NO:14:

20

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 169 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - 25 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

35 Met His Leu Ala Arg Leu Val Gly Ser Cys Ser Leu Leu Leu Leu Leu
 1 5 10 15
 Gly Ala Leu Ser Gly Trp Ala Ala Ser Asp Asp Pro Ile Glu Lys Val
 20 25 30
 40 Ile Glu Gly Ile Asn Arg Gly Leu Ser Asn Ala Glu Arg Glu Val Gly
 35 40 45
 Lys Ala Leu Asp Gly Ile Asn Ser Gly Ile Thr His Ala Gly Arg Glu
 50 55 60
 45 Val Glu Lys Val Phe Asn Gly Leu Ser Asn Met Gly Ser His Thr Gly
 65 70 75 80
 50 Lys Glu Leu Asp Lys Gly Val Gln Gly Leu Asn His Gly Met Asp Lys
 85 90 95
 Val Ala His Glu Ile Asn His Gly Ile Gly Gln Ala Gly Lys Glu Ala
 100 105 110
 55 Glu Lys Leu Gly His Gly Val Asn Asn Ala Ala Gly Gln Gly Asn His

	115		120		125
	Gln Ser Gly Ser Ser Ser His Gln Gly Gly Ala Thr Thr Thr Pro Leu				
	130		135		140
5	Ala Ser Gly Ala Ser Val Asn Thr Pro Phe Ile Asn Leu Pro Ala Leu				
	145		150		155
	Trp Arg Ser Val Ala Asn Ile Met Pro				
10			165		

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

15 (A) LENGTH: 1240 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: cDNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

	AATGGCTTTT CTCCTTCCT GGGTTTGTGT ACTAGTTGGT TCCTTTTCTG CTCCTTAGC	60
	AGGGACTTCC AATCTCTCAG AGACAGAGCC CCCTCTGTGG AAGGAGAGTC CTGGTCAGCT	120
30	CAGTGA CTAC AGGGTGGAGA ACAGCATGTA CATTATTAAT CCCTGGGTAT ACCTTGAGAG	180
	AATGGGGATG TATAAAATCA TATTGAATCA GACAGCCAGG TATTTTGCAA AATTTGCACC	240
35	AGATAATGAA CAGAATATTT TATGGGGGTT GCCTCTGCAG TATGGCTGGC AATATAGGAC	300
	AGGCAGATTA GCTGATCCAA CCCGAAGGAC AAAGTGTGGC TATGAATCTG GAGATCATAT	360
	GTGCATCTCT GTGGACAGTT GGTGGGCTGA TTTGAATTAT TTTCTGTCTT CATTACCCTT	420
40	TCTTGCTGCG GTTGATTCTG GTGTAATGGG GATATCATCA GACCAAGTCA GGCTTTTGCC	480
	CCCACCCAAG AATGAGAGGA AGTTTTGTTA TGATGTTTCT AGCTGTCGTT CATCCTTCCC	540
45	TGAGACAATG AACAAGTGGA ACACCTTTTA CCAGTATTTG CAGTCACCTT TTAGTAAGTT	600
	TGATGATCTG TTGAAGTACT TATGGGCTGC ACACACTTCA ACCTTGGCAG ATAATATCAA	660
	AAGTTTGTAA GACAGATATG ATTATTATTC TAAAGCAGAA GCGCATTTTG AGAGAAGTTG	720
50	GGTACTGGCT GTGGATCATT TAGCTGCAGT CCTCTTTCCT ACAACCTTGA TTAGATCATA	780
	TAAGTTCCAG AAGGGCATGC CACCACGAAT TCTTCTTAAT ACTGATGTAG CCCCTTTCAT	840
55	CAGTGA CTTT ACTGCTTTTC AGAATGTAGT CCTGGTTCTT CTAAATATGC TTGACAATGT	900

GGATAAATCT ATAGGTTATC TTTGTACAGA AAAATCTAAT GTATATAGAG ATCATTTCGGA 960
 ATCTAGCTCT AGAAGTTATG GAAATAACTC CTGAAACATT TAACTTCAAA CTTCAGGAAA 1020
 5 TGATTAATGA ATTAAAAATG AAAAAGCTCGA ACTTGACAAT CAGTAATTTT AAAAAATTAA 1080
 TGTCATCATG ACCATGTAGT TTATTCTTTC TGATATTTTT GATTTATGCT TATTTGTTAA 1140
 10 GATCTTGTAC ATGTATTAAA AACTTAAATT AAATGCATTC AAGTTAAAAA AAAAAAAAAA 1200
 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1240

(2) INFORMATION FOR SEQ ID NO:16:

15 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 330 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Ala Phe Leu Pro Ser Trp Val Cys Val Leu Val Gly Ser Phe Ser
 1 5 10 15
 30 Ala Ser Leu Ala Gly Thr Ser Asn Leu Ser Glu Thr Glu Pro Pro Leu
 20 25 30
 35 Trp Lys Glu Ser Pro Gly Gln Leu Ser Asp Tyr Arg Val Glu Asn Ser
 35 40 45
 Met Tyr Ile Ile Asn Pro Trp Val Tyr Leu Glu Arg Met Gly Met Tyr
 50 55 60
 40 Lys Ile Ile Leu Asn Gln Thr Ala Arg Tyr Phe Ala Lys Phe Ala Pro
 65 70 75 80
 Asp Asn Glu Gln Asn Ile Leu Trp Gly Leu Pro Leu Gln Tyr Gly Trp
 85 90 95
 45 Gln Tyr Arg Thr Gly Arg Leu Ala Asp Pro Thr Arg Arg Thr Asn Cys
 100 105 110
 Gly Tyr Glu Ser Gly Asp His Met Cys Ile Ser Val Asp Ser Trp Trp
 115 120 125
 50 Ala Asp Leu Asn Tyr Phe Leu Ser Ser Leu Pro Phe Leu Ala Ala Val
 130 135 140
 55 Asp Ser Gly Val Met Gly Ile Ser Ser Asp Gln Val Arg Leu Leu Pro

	145		150		155		160									
	Pro	Pro	Lys	Asn	Glu	Arg	Lys	Phe	Cys	Tyr	Asp	Val	Ser	Ser	Cys	Arg
				165						170					175	
5	Ser	Ser	Phe	Pro	Glu	Thr	Met	Asn	Lys	Trp	Asn	Thr	Phe	Tyr	Gln	Tyr
				180					185					190		
10	Leu	Gln	Ser	Pro	Phe	Ser	Lys	Phe	Asp	Asp	Leu	Leu	Lys	Tyr	Leu	Trp
			195					200					205			
	Ala	Ala	His	Thr	Ser	Thr	Leu	Ala	Asp	Asn	Ile	Lys	Ser	Phe	Glu	Asp
		210					215					220				
15	Arg	Tyr	Asp	Tyr	Tyr	Ser	Lys	Ala	Glu	Ala	His	Phe	Glu	Arg	Ser	Trp
	225					230					235					240
	Val	Leu	Ala	Val	Asp	His	Leu	Ala	Ala	Val	Leu	Phe	Pro	Thr	Thr	Leu
				245						250					255	
20	Ile	Arg	Ser	Tyr	Lys	Phe	Gln	Lys	Gly	Met	Pro	Pro	Arg	Ile	Leu	Leu
			260						265					270		
	Asn	Thr	Asp	Val	Ala	Pro	Phe	Ile	Ser	Asp	Phe	Thr	Ala	Phe	Gln	Asn
25			275					280					285			
	Val	Val	Leu	Val	Leu	Leu	Asn	Met	Leu	Asp	Asn	Val	Asp	Lys	Ser	Ile
		290					295					300				
30	Gly	Tyr	Leu	Cys	Thr	Glu	Lys	Ser	Asn	Val	Tyr	Arg	Asp	His	Ser	Glu
	305					310					315					320
	Ser	Ser	Ser	Arg	Ser	Tyr	Gly	Asn	Asn	Ser						
				325						330						

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2261 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

50	GCAGCACCAG	CCGTCTGCAG	CTCCGGCCGC	CACTTGCGCC	TCTCCAGCCT	CCGCAGGCCC	60
	AACCGCCGCC	AGCACCATGG	CCAGCACCAT	TTCCGCCTAC	AAGGAGAAGA	TGAAGGAGCT	120
55	GTCGGTGCTG	TCGCTCATCT	GCTCCTGCTT	CTACACACAG	CCGCACCCCA	ATACCGTCTA	180

	CCAGTACGGG GACATGGAGG TGAAGCAGCT GGACAAGCGG GCCTCAGGCC AGAGCTTCGA	240
	GGTCATCCTC AAGTCCCCTT CTGACCTGTC CCCAGAGAGC CCTATGCTCT CCTCCCCACC	300
5	CAAGAAGAAG GACACCTCCC TGGAGGAGCT GCAAAAGCGG CTGGAGGCAG CCGAGGAGCG	360
	GAGGAAGACG CAGGAGGCGC AGGTGCTGAA GCAGCTGGCG GAGCGGCGCG AGCACGAGCG	420
10	CGAGGTGCTG CACAAGGCGC TGGAGGAGAA TAACAACCTC AGCCGCCAGG CGGAGGAGAA	480
	GCTCAACTAC AAGATGGAGC TCAGCAAGGA GATCCGCGAG GCACACCTGG CCGCACTGCG	540
	CGAGCGGCTG CGCGAGAAGG AGCTGCACGC GGCCGAGGTG CGCAGGAACA AGGAGCAGCG	600
15	AGAAGAGATG TCGGGCTAAG GGCCCGGGAC GGGCGGCGCC CATCCTGCGA CAGAACACGT	660
	TCGGGTTTTG GTTTTGTTC GTTCACCTCT GTCTAGATGC AACTTTTGT TCTCCTCCCC	720
20	CACCCAGCC CCCAGCTTCA TGCTTCTCTT CCGCACTCAG CCGCCCTGCC CTGTCTCTCGT	780
	GGTGAGTCGC TGACCACGGC TTCCCTTGCA GGAGCCGCCG GGCCTGAGAC GCGGTCCCTC	840
	GGTGCAGACA CCAGGCCGGG CGCGCTGGG TCCCCGGGG GCCCTGTGAG AGAGGTGGCG	900
25	GTGACCGTGG TAAACCCAGG GCGGTGGCGT GGGATCGCGG GTCCTTACGC TGGGCTGTCT	960
	GGTCAGCACG TGCAGGTCAG GGCAGGTCC TGTAGCCGGC GCCCTTGGCC AGCAGGCGAG	1020
30	GCTACAGTAC CTGCTGTCTT TCCAGGGGGA AGGGGCTCCC CATGAGGGAG GGGCGACGGG	1080
	GGAGGGGGGT GATGGTGCCT GGGAGCCTGC GTGTGCAGCC GGTGCTTGT TGAAGTGGCAG	1140
	GCGGGTGGGT GGGGGCTGCA GCTTTCCCTTA ATGTGGTTGC ACAGGGGTCC TCTGAGACCA	1200
35	CCTGGCGTGA GGTGGACACC CTGGGCCCTT CTGGAAGCCT GCAGTTGGGG GCCTGCCCTG	1260
	AGTCTGCTGG GGAGTGGCA TTCTCTGCCA GGGACCCATG AGCAGGCTGC ATGGTCTAGA	1320
40	GGTTGTGGGC AGCATGGACA GTCCCCACT CAGAAAGTGA AGAGTTCCAA AGAGCCTCTG	1380
	GCCCAGGCCC CTCCCCACCA GGGCTTTGCA GATGTCCTTG AAAGACCCAC CCTAGAGCCC	1440
	TTTGGAGTGC TGGCCCTCC TGTGCCCTCT GCCCTGGTGG AAGCGGCAGC CACAAGTCCT	1500
45	CCTCAGGGAG CCCCAAGGGG GATTTTGTGG GACCGCTGCC CACAGATCCA GGTGTTGGAA	1560
	GGGCAGCGGG TAAGGTTCCC AAGCCAGCCC CAACACCCCT CCCACTTGGC ACCCAGAGGG	1620
50	GGCTGTGGGT GGAGGCCCTG CTCCAGGCC TCTCTGCCCA CACCCTCTGG GCTGAGTTCC	1680
	TTCTTTCCCT TGGACGCCCA GTGCTGGCCT TGGAGGACGG TCAGCTGGAG GATGGCGGTG	1740
	GGGGAGGCTG TCTTTGTACC ACTGCAGCAT CCCCCACTTC TCCACGGAAG CCCCATCCCA	1800
55	AAGCTGCTGC CTGGCCCTT GCTGTAAAGT GTGAAGGGGG CGGCTGAGTT CTCTTAGGAC	1860

CCAGAGCCAG GGCCCTCAAC TTCCATCCTG CGGGAGGCCT TGGCCGGGCA CTGCCAGTGT 1920
 CTTCCAGAGC CACACCCAGG GACCACGGGA GGATCCTGAC CCCTGCAGGG CTCAGGGGTC 1980
 5 AGCAGGGACC CACTGCCCCA TCTCCCTCTC CCCACCAAGA CAGCCCCAGA AGGAGCAGCC 2040
 AGCTGGGATG GGAACCCAAG GCTGTCCACA TCTGGCTTTT GTGGGACTCA GAAAGGGAAG 2100
 CAGAACTGAG GGCTGGGATA TTCCTCATGG TGGCAGCGCT CATAGCGAAA GCCTACTGTA 2160
 10 ATATGCACCC ATCTCATCCA CGTAGTAAAG TGAACCTAAA AATTCAATCA AATGAACAAT 2220
 TAAATAAACA CCTGTGTGTT TAAGAAAAAA AAAAAAAAAA A 2261

15 (2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 180 amino acids

(B) TYPE: amino acid

20 (C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

30 Met Ala Ser Thr Ile Ser Ala Tyr Lys Glu Lys Met Lys Glu Leu Ser
 1 5 10 15
 Val Leu Ser Leu Ile Cys Ser Cys Phe Tyr Thr Gln Pro His Pro Asn
 20 25 30
 35 Thr Val Tyr Gln Tyr Gly Asp Met Glu Val Lys Gln Leu Asp Lys Arg
 35 40 45
 Ala Ser Gly Gln Ser Phe Glu Val Ile Leu Lys Ser Pro Ser Asp Leu
 40 50 55 60
 Ser Pro Glu Ser Pro Met Leu Ser Ser Pro Pro Lys Lys Lys Asp Thr
 65 70 75 80
 45 Ser Leu Glu Glu Leu Gln Lys Arg Leu Glu Ala Ala Glu Glu Arg Arg
 85 90 95
 Lys Thr Gln Glu Ala Gln Val Leu Lys Gln Leu Ala Glu Arg Arg Glu
 100 105 110
 50 His Glu Arg Glu Val Leu His Lys Ala Leu Glu Glu Asn Asn Asn Phe
 115 120 125
 Ser Arg Gln Ala Glu Glu Lys Leu Asn Tyr Lys Met Glu Leu Ser Lys
 55 130 135 140

Glu Ile Arg Glu Ala His Leu Ala Ala Leu Arg Glu Arg Leu Arg Glu
 145 150 155 160
 Lys Glu Leu His Ala Ala Glu Val Arg Arg Asn Lys Glu Gln Arg Glu
 5 165 170 175
 Glu Met Ser Gly
 180

10 (2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3109 base pairs
 (B) TYPE: nucleic acid
 15 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

25 GGCCAAAGAG GCCTAGGAGC CTCGTGGCTG CGTCACCGCC GCCCCCCCAG ACAAGATGGA 60
 CACCGCGGAG GAAGACATAT GTAGAGTGTG TCGGTCAGAA GGAACACCTG AGAAACCGCT 120
 TTATCATCCT TGTGTATGTA CTGGCAGTAT TAAGTTTATC CATCAAGAAT GCTTAGTTCA 180
 30 ATGGCTGAAA CACAGTCGAA AAGAATACTG TGAATTATGC AAGCACAGAT TTGCTTTTAC 240
 ACCAATTTAT TCTCCAGATA TGCCTTCACG GCTTCCAATT CAAGACATAT TTGCTGGACT 300
 35 GGTTACAAGT ATTGGCACTG CAATACGATA TTGGTTTCAT TATACACTTG TGGCCTTTGC 360
 ATGGTTGGGA GTTGTTCCTC TTACAGCATG CCGCATCTAC AAGTGCTTGT TTACTGGCTC 420
 CCGTGAGCTC ACTACTGACG CTGCCCATTA GATATGCTGT CAACCGGAAA ATTTGTTGGC 480
 40 AGATTGTTTG CAGGGTTGTT TTGTGGTGAC GTGCACACTG TGTGCATTCA TCAGCCTGGT 540
 GTGGTTGAGA GAGCAGATAG TCCATGGGGG AGCACCAATT TGGTTGGAGC ATGCTGCCCC 600
 45 ACCGTTCAAT GCTGCGGGGC ATCACCAAAA TGAGGCTCCA GCAGGAGGAA ATGGTGCAGA 660
 AAATGTTGCT GCTGATCAGC CTGCTAACCC ACCAGCTGAG AACGCAGTGG TGGGGGAAAA 720
 CCCTGATGCC CAGGATGACC AGGCAGAAGA GGAGGAGGAG GACAATGAGG AGGAAGATGA 780
 50 CGCTGGTGTG GAGGATGGCG GCAGATGCTA ATAACGGAGC CCAGGATGAC ATGAATTGGA 840
 ATGCTTTAGA ATGGGACCGA GCTGCTGAAG AGCTTACATG GGAAAGAATG CTAGGACTTG 900
 55 ATGGATCACT AGTTTTTCTG GAACATGTCT TCTGGGTGGT ATCTTTAAAT ACACTGTTCA 960

	TTCTTGTTTT TGCATTTTGC CCTTACCATA TTGGTCATTT CTCCCTTGTT GGTTTGGGAT	1020
	TTGAAGAACA CGTCCAAGCA TCTCATTTTG AAGGCCTAAT CACAACCATA GTTGGGTATA	1080
5	TACTTTTAGC AATAACACTG ATAATTTGTC ATGGCTTGGC AACTCTTGTTG AAATTTTCATA	1140
	GATCTCGTCG CTTACTGGGA GTCTGCTATA TTGTTGTTAA GGTCTCTTTG TTAGTGGTGG	1200
	TAGAAATTGG AGTATTCCTT CTCATTTGTG GTTGGTGGCT GGATATCTGT TCCTTGAAAA	1260
10	TGTTTGATGC TACTCTGAAA GATCGAGAAC TGAGCTTTCA GTCGGCTCCA GGTACTACCA	1320
	TGTTTCTGCA TTGGCTAGTG GGAATGGTAT ATGTCTTCTA CTTTGCCTCC TTCATTCTAT	1380
15	TACTGAGAGA GGTACTTCGA CCTGGTGTCC TGTGGTTTCT AAGGAATTTG AATGATCCAG	1440
	ATTTCAATCC AGTACAGGAA ATGATCCATT TGCCAATATA TAGGCATCTC CGAAGATTTA	1500
	TTTTGTCAGT GATTGTCTTT GGCTCCATTG TCCTCCTGAT GCTTTGGCTT CCTATACGTA	1560
20	TAATTAAGAG TGTGCTGCCT AATTTTCTTC CATACAATGT CATGCTCTAC AGTGATGCTC	1620
	CAGTGAGTGA ACTGTCCCTC GAGCTGCTTC TGCTTCAGGT TGTCTTGCCA GCATTACTCG	1680
25	AACAGGGACA CACGAGGCAG TGGCTGAAGG GGCTGGTGGC AGCGTGGACT GTGACCGCCG	1740
	GATACTTGCT GGATCTTCAT TCTTATTTAT TGGGAGACCA GGAAGAAAAT GAAAACAGTG	1800
	CAAATCAACA AGTTAACAAT AATCAGCATG CTCGAAATAA CAACGCTATT CCTGTGGTGG	1860
30	GAGAAGGCCT TCATGCAGCC CACCAAGCCA TACTCCAGCA GGGAGGGCCT GTTGGCTTTC	1920
	AGCCTTACCG CCGACCTTTA AATTTTCCAC TCAGGATATT TCTGTTGATT GTCTTCATGT	1980
35	GTATAACATT ACTGATTGCC AGCCTCATCT GCCTTACTTT ACCAGTATTT GCTGGCCGTT	2040
	GGTTAATGTC GTTTTGGACG GGGACTGCCA AAATCCATGA GCTCTACACA GCTGCTTGTC	2100
	GTCTCTATGT TTGCTGGCTA ACCATAAGGG CTGTGACGGT GATGGTGGCA TGGATGCCTC	2160
40	AGGGACGCAG AGTGATCTTC CAGAAGGTTA AAGAGTGGTC TCTCATGATC ATGAAGACTT	2220
	TGATAGTTGC GGTGCTGTTG GCTGGAGTTG TCCCTCTCCT TCTGGGGCTC CTGTTTGAGC	2280
45	TGGTCATTGT GGCTCCCCTG AGGGTTCCCT TGGATCAGAC TCCTCTTTTT TATCCATGGC	2340
	AGGACTGGGC ACTTGGAGTC CTGCATGCCA AAATCATTGC AGCTATAACA TTGATGGGTC	2400
	CTCAGTGGTG GTTGAAAACCT GTAATTGAAC AGGTTTACGC AAATGGCATC CGGAACATTG	2460
50	ACCTTCACTA TATTGTTCGT AACTGGCAG CTCCCGTGAT CTCTGTGCTG TTGCTTTCCC	2520
	TGTGTGTACC TTATGTCATA GCTTCTGGTG TTGTTCCCTT ACTAGGTGTT ACTGCGGAAA	2580
55	TGCAAACTT AGTCCATCGG CGGATTTATC CATTTTTACT GATGGTCGTG GTATTGATGG	2640

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CAATTTTGTG CTTCCAAGTC CGCCAGTTTA AGCGCCTTTA TGAACATATT AAAAATGACA 2700
AGTACCTTGK GGGTCAASGA CTCGGTGAAC TACGAACGGA AATCTGGGCA AACAAGGCTC 2760
5 ATCTCCACCA CCTCCACAGT CATCCCAAGA ATAAAGTAGT TGTCTCAACA ACTTGACCTT 2820
CCCCTTTACA TGTCCTTTTT TGTGGACTTC TCTCTTKGGA GATTTTTCCT AGTGATCTCT 2880
CAGCGTKGTT TTTAAGTTAA AKGTATTGGA CTTGTGTTCT CAGCATTCAG AGAGCAGCGG 2940
10 TGTAAGATTC TGCTGTTCTC CCTGGATCTT CTGACATKAC TGCTGTCTGA GATTTGTATA 3000
TGKGTAAATA CAAGTTCCTT GATACCCTAA AACCTTGGAT TAAACAGAAT GTGCATKGTA 3060
15 CATCTTTAAA CAAAATGKAT ATTAATTTAT TAAAAAATAA AAAAAAATAA 3109

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(2) INFORMATION FOR SEQ ID NO:20:

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20 (i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 750 amino acids
    (B) TYPE: amino acid
    (C) STRANDEDNESS:
    (D) TOPOLOGY: linear

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25 (ii) MOLECULE TYPE: protein

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30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

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Met Gly Glu His Gln Phe Gly Trp Ser Met Leu Pro His Arg Ser Met
1           5           10           15
35 Leu Arg Gly Ile Thr Lys Met Arg Leu Gln Gln Glu Glu Met Val Gln
    20           25           30
40 Lys Met Leu Leu Leu Ile Ser Leu Leu Thr His Gln Leu Arg Thr Gln
    35           40           45
    Trp Trp Gly Lys Thr Leu Met Pro Arg Met Thr Arg Gln Lys Arg Arg
    50           55           60
45 Arg Arg Thr Met Arg Arg Lys Met Thr Leu Val Trp Arg Met Ala Ala
    65           70           75           80
    Asp Ala Asn Asn Gly Ala Gln Asp Asp Met Asn Trp Asn Ala Leu Glu
    85           90           95
50 Trp Asp Arg Ala Ala Glu Glu Leu Thr Trp Glu Arg Met Leu Gly Leu
    100          105          110
    Asp Gly Ser Leu Val Phe Leu Glu His Val Phe Trp Val Val Ser Leu
    115          120          125
55

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	Asn Thr Leu Phe Ile Leu Val Phe Ala Phe Cys Pro Tyr His Ile Gly	
	130	135 140
5	His Phe Ser Leu Val Gly Leu Gly Phe Glu Glu His Val Gln Ala Ser	
	145	150 155 160
	His Phe Glu Gly Leu Ile Thr Thr Ile Val Gly Tyr Ile Leu Leu Ala	
		165 170 175
10	Ile Thr Leu Ile Ile Cys His Gly Leu Ala Thr Leu Val Lys Phe His	
		180 185 190
	Arg Ser Arg Arg Leu Leu Gly Val Cys Tyr Ile Val Val Lys Val Ser	
		195 200 205
15	Leu Leu Val Val Val Glu Ile Gly Val Phe Pro Leu Ile Cys Gly Trp	
		210 215 220
20	Trp Leu Asp Ile Cys Ser Leu Glu Met Phe Asp Ala Thr Leu Lys Asp	
		225 230 235 240
	Arg Glu Leu Ser Phe Gln Ser Ala Pro Gly Thr Thr Met Phe Leu His	
		245 250 255
25	Trp Leu Val Gly Met Val Tyr Val Phe Tyr Phe Ala Ser Phe Ile Leu	
		260 265 270
	Leu Leu Arg Glu Val Leu Arg Pro Gly Val Leu Trp Phe Leu Arg Asn	
		275 280 285
30	Leu Asn Asp Pro Asp Phe Asn Pro Val Gln Glu Met Ile His Leu Pro	
		290 295 300
35	Ile Tyr Arg His Leu Arg Arg Phe Ile Leu Ser Val Ile Val Phe Gly	
		305 310 315 320
	Ser Ile Val Leu Leu Met Leu Trp Leu Pro Ile Arg Ile Ile Lys Ser	
		325 330 335
40	Val Leu Pro Asn Phe Leu Pro Tyr Asn Val Met Leu Tyr Ser Asp Ala	
		340 345 350
	Pro Val Ser Glu Leu Ser Leu Glu Leu Leu Leu Leu Gln Val Val Leu	
		355 360 365
45	Pro Ala Leu Leu Glu Gln Gly His Thr Arg Gln Trp Leu Lys Gly Leu	
		370 375 380
50	Val Arg Ala Trp Thr Val Thr Ala Gly Tyr Leu Leu Asp Leu His Ser	
		385 390 395 400
	Tyr Leu Leu Gly Asp Gln Glu Glu Asn Glu Asn Ser Ala Asn Gln Gln	
		405 410 415
55	Val Asn Asn Asn Gln His Ala Arg Asn Asn Asn Ala Ile Pro Val Val	

	420	425	430
	Gly Glu Gly Leu His Ala Ala His Gln Ala Ile Leu Gln Gln Gly Gly		
	435	440	445
5	Pro Val Gly Phe Gln Pro Tyr Arg Arg Pro Leu Asn Phe Pro Leu Arg		
	450	455	460
10	Ile Phe Leu Leu Ile Val Phe Met Cys Ile Thr Leu Leu Ile Ala Ser		
	465	470	475
	Leu Ile Cys Leu Thr Leu Pro Val Phe Ala Gly Arg Trp Leu Met Ser		
	485	490	495
15	Phe Trp Thr Gly Thr Ala Lys Ile His Glu Leu Tyr Thr Ala Ala Cys		
	500	505	510
	Gly Leu Tyr Val Cys Trp Leu Thr Ile Arg Ala Val Thr Val Met Val		
	515	520	525
20	Ala Trp Met Pro Gln Gly Arg Arg Val Ile Phe Gln Lys Val Lys Glu		
	530	535	540
25	Trp Ser Leu Met Ile Met Lys Thr Leu Ile Val Ala Val Leu Leu Ala		
	545	550	555
	Gly Val Val Pro Leu Leu Leu Gly Leu Leu Phe Glu Leu Val Ile Val		
	565	570	575
30	Ala Pro Leu Arg Val Pro Leu Asp Gln Thr Pro Leu Phe Tyr Pro Trp		
	580	585	590
	Gln Asp Trp Ala Leu Gly Val Leu His Ala Lys Ile Ile Ala Ala Ile		
	595	600	605
35	Thr Leu Met Gly Pro Gln Trp Trp Leu Lys Thr Val Ile Glu Gln Val		
	610	615	620
40	Tyr Ala Asn Gly Ile Arg Asn Ile Asp Leu His Tyr Ile Val Arg Lys		
	625	630	635
	Leu Ala Ala Pro Val Ile Ser Val Leu Leu Leu Ser Leu Cys Val Pro		
	645	650	655
45	Tyr Val Ile Ala Ser Gly Val Val Pro Leu Leu Gly Val Thr Ala Glu		
	660	665	670
	Met Gln Asn Leu Val His Arg Arg Ile Tyr Pro Phe Leu Leu Met Val		
	675	680	685
50	Val Val Leu Met Ala Ile Leu Ser Phe Gln Val Arg Gln Phe Lys Arg		
	690	695	700
55	Leu Tyr Glu His Ile Lys Asn Asp Lys Tyr Leu Xaa Gly Gln Xaa Leu		
	705	710	715
			720

Gly Glu Leu Arg Thr Glu Ile Trp Ala Asn Lys Ala His Leu His His
725 730 735

5 Leu His Ser His Pro Lys Asn Lys Val Val Val Ser Thr Thr
740 745 750

(2) INFORMATION FOR SEQ ID NO:21:

- 10 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 15 (ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TNTTTGAAGT TTCTCCCTCT CATTCTGAG 29

25 (2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
30 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

35

- 40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GNTTCTCCAC GTAGTTGGTT TTCCTCAGT 29

(2) INFORMATION FOR SEQ ID NO:23:

- 45 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 50 (ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

55

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CNACATGACG TGAGCTGGTG ATCCATGAA

29

5 (2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

15 (A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

20

ANTTGGGCTC TGCCGTCCAG AAAGGTTTG

29

(2) INFORMATION FOR SEQ ID NO:25:

25 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

GNAGCTACGC GGACTTGCAG AGGTTTTAT

40

29

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs

45 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

50 (A) DESCRIPTION: /desc = "oligonucleotide"

55

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TNGGTGAGAG AATAGAGACT GGCTGGGAA

29

(2) INFORMATION FOR SEQ ID NO:27:

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10

- (ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

ANGAGCCGAC CAGACGTGCA AGATGCATA

29

20

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25

- (ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

30

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

ANCTGACCAG GACTCTCCTT CCACAGAGG

29

40

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

45

- (ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

50

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

55 TNTAGGCGGA AATGGTGCTG GCCATGGTG

29

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

- 10 (A) DESCRIPTION: /desc = "oligonucleotide"

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

ANATATCCAG CCACCAACCA CAAATGAGA

29

What is claimed is:

1. An isolated polynucleotide selected from the group consisting of:
 - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 185 to nucleotide 1600;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1403 to nucleotide 1600;
 - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 850;
 - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone do15_4 deposited under accession number ATCC 98468;
 - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone do15_4 deposited under accession number ATCC 98468;
 - (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone do15_4 deposited under accession number ATCC 98468;
 - (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone do15_4 deposited under accession number ATCC 98468;
 - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;
 - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:2;
 - (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
 - (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
 - (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).
2. The polynucleotide of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.

3. A host cell transformed with the polynucleotide of claim 2.
4. The host cell of claim 3, wherein said cell is a mammalian cell.
5. A process for producing a protein encoded by the polynucleotide of claim 2, which process comprises:
 - (a) growing a culture of the host cell of claim 3 in a suitable culture medium; and
 - (b) purifying said protein from the culture.
6. A protein produced according to the process of claim 5.
7. A protein comprising an amino acid sequence selected from the group consisting of:
 - (a) the amino acid sequence of SEQ ID NO:2;
 - (b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 222;
 - (c) fragments of the amino acid sequence of SEQ ID NO:2 comprising eight consecutive amino acids of SEQ ID NO:2; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone do15_4 deposited under accession number ATCC 98468;the protein being substantially free from other mammalian proteins.
8. The protein of claim 7, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.
9. The protein of claim 7, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 222.
10. A composition comprising the protein of claim 7 and a pharmaceutically acceptable carrier.
11. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.

12. An isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 47 to nucleotide 2065;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1086 to nucleotide 1848;
 - (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone dx290_1 deposited under accession number ATCC 98468;
 - (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone dx290_1 deposited under accession number ATCC 98468;
 - (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone dx290_1 deposited under accession number ATCC 98468;
 - (g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone dx290_1 deposited under accession number ATCC 98468;
 - (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;
 - (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:4;
 - (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
 - (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
 - (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).
13. A protein comprising an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:4;
 - (b) the amino acid sequence of SEQ ID NO:4 from amino acid 312 to amino acid 600;

- (c) fragments of the amino acid sequence of SEQ ID NO:4 comprising eight consecutive amino acids of SEQ ID NO:4; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone dx290_1 deposited under accession number ATCC 98468;
- the protein being substantially free from other mammalian proteins.

14. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.
15. An isolated polynucleotide selected from the group consisting of:
 - (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 107 to nucleotide 724;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 218 to nucleotide 724;
 - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 536 to nucleotide 866;
 - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ek390_4 deposited under accession number ATCC 98468;
 - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ek390_4 deposited under accession number ATCC 98468;
 - (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ek390_4 deposited under accession number ATCC 98468;
 - (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ek390_4 deposited under accession number ATCC 98468;
 - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;
 - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:6;
 - (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

16. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 6 to amino acid 92;

(c) fragments of the amino acid sequence of SEQ ID NO:6 comprising eight consecutive amino acids of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone ek390_4 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins.

17. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

18. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 31 to nucleotide 1230;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 289 to nucleotide 1230;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 344 to nucleotide 1119;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone er471_7 deposited under accession number ATCC 98468;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone er471_7 deposited under accession number ATCC 98468;

(g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone er471_7 deposited under accession number ATCC 98468;

(h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone er471_7 deposited under accession number ATCC 98468;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:8;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

19. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 111 to amino acid 363;

(c) fragments of the amino acid sequence of SEQ ID NO:8 comprising eight consecutive amino acids of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone er471_7 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins.

20. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

21. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 62 to nucleotide 322;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 571 to nucleotide 878;
- (d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone fs40_3 deposited under accession number ATCC 98468;
- (e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone fs40_3 deposited under accession number ATCC 98468;
- (f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone fs40_3 deposited under accession number ATCC 98468;
- (g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone fs40_3 deposited under accession number ATCC 98468;
- (h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;
- (i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:10;
- (j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;
- (k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and
- (l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i).

22. A protein comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:10;
 - (b) fragments of the amino acid sequence of SEQ ID NO:10 comprising eight consecutive amino acids of SEQ ID NO:10; and
 - (c) the amino acid sequence encoded by the cDNA insert of clone fs40_3 deposited under accession number ATCC 98468;
- the protein being substantially free from other mammalian proteins.

23. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.
24. An isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 43 to nucleotide 1671;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 112 to nucleotide 1671;
 - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 224 to nucleotide 679;
 - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ga63_6 deposited under accession number ATCC 98468;
 - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ga63_6 deposited under accession number ATCC 98468;
 - (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ga63_6 deposited under accession number ATCC 98468;
 - (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ga63_6 deposited under accession number ATCC 98468;
 - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;
 - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:12;
 - (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
 - (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
 - (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

25. A protein comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:12;
- (b) the amino acid sequence of SEQ ID NO:12 from amino acid 62 to amino acid 212;
- (c) fragments of the amino acid sequence of SEQ ID NO:12 comprising eight consecutive amino acids of SEQ ID NO:12; and
- (d) the amino acid sequence encoded by the cDNA insert of clone ga63_6 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins.

26. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:11.

27. An isolated polynucleotide selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;
- (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 17 to nucleotide 523;
- (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 77 to nucleotide 523;
- (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1 to nucleotide 392;
- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone gm335_4 deposited under accession number ATCC 98468;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone gm335_4 deposited under accession number ATCC 98468;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone gm335_4 deposited under accession number ATCC 98468;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone gm335_4 deposited under accession number ATCC 98468;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:14;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

28. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 125;

(c) fragments of the amino acid sequence of SEQ ID NO:14 comprising eight consecutive amino acids of SEQ ID NO:14; and

(d) the amino acid sequence encoded by the cDNA insert of clone gm335_4 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins.

29. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.

30. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 2 to nucleotide 991;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 62 to nucleotide 991;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 2 to nucleotide 504;

- (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone hy370_9 deposited under accession number ATCC 98468;
- (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone hy370_9 deposited under accession number ATCC 98468;
- (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone hy370_9 deposited under accession number ATCC 98468;
- (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone hy370_9 deposited under accession number ATCC 98468;
- (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;
- (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:16;
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

31. A protein comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:16;
- (b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 167;
- (c) fragments of the amino acid sequence of SEQ ID NO:16 comprising eight consecutive amino acids of SEQ ID NO:16; and
- (d) the amino acid sequence encoded by the cDNA insert of clone hy370_9 deposited under accession number ATCC 98468;

the protein being substantially free from other mammalian proteins.

32. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

33. An isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 77 to nucleotide 616;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 164 to nucleotide 616;
 - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 415;
 - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ie47_4 deposited under accession number ATCC 98468;
 - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ie47_4 deposited under accession number ATCC 98468;
 - (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ie47_4 deposited under accession number ATCC 98468;
 - (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ie47_4 deposited under accession number ATCC 98468;
 - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;
 - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:18;
 - (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
 - (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
 - (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).
34. A protein comprising an amino acid sequence selected from the group consisting of:
- (a) the amino acid sequence of SEQ ID NO:18;

- (b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 113;
 - (c) fragments of the amino acid sequence of SEQ ID NO:18 comprising eight consecutive amino acids of SEQ ID NO:18; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone ie47_4 deposited under accession number ATCC 98468;
- the protein being substantially free from other mammalian proteins.

35. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:17.
36. An isolated polynucleotide selected from the group consisting of:
- (a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;
 - (b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 564 to nucleotide 2813;
 - (c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 705 to nucleotide 2813;
 - (d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 793 to nucleotide 1628;
 - (e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone s195_10 deposited under accession number ATCC 98468;
 - (f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone s195_10 deposited under accession number ATCC 98468;
 - (g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone s195_10 deposited under accession number ATCC 98468;
 - (h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone s195_10 deposited under accession number ATCC 98468;
 - (i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;
 - (j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising eight consecutive amino acids of SEQ ID NO:20;

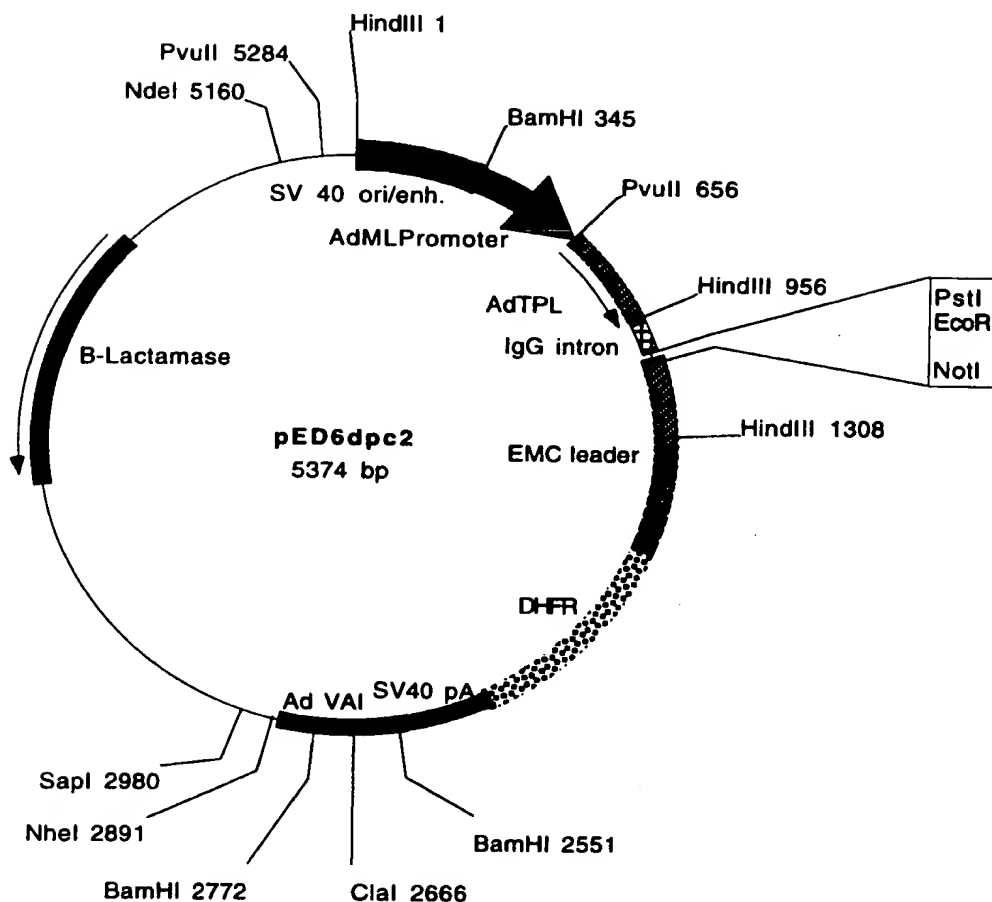
- (k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;
- (l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and
- (m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j).

37. A protein comprising an amino acid sequence selected from the group consisting of:

- (a) the amino acid sequence of SEQ ID NO:20;
 - (b) the amino acid sequence of SEQ ID NO:20 from amino acid 78 to amino acid 355;
 - (c) fragments of the amino acid sequence of SEQ ID NO:20 comprising eight consecutive amino acids of SEQ ID NO:20; and
 - (d) the amino acid sequence encoded by the cDNA insert of clone s195_10 deposited under accession number ATCC 98468;
- the protein being substantially free from other mammalian proteins.

38. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:19.

FIGURE 1A

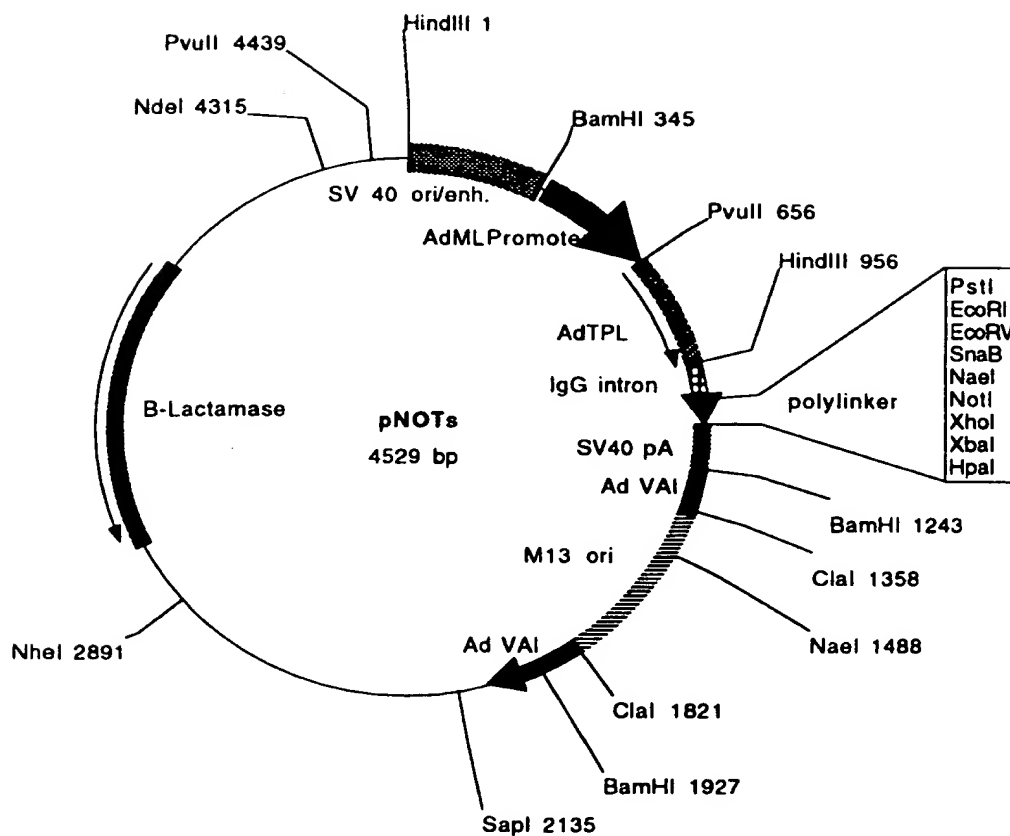


Plasmid name: pED6dpc2

Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs

Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al, 1989. Mol. Cell. Biol. 9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the Clal site. SST cDNAs are cloned between EcoRI and NotI

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/12516

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C 07K 1/00; C07H 21/02; A61K 39/00; C12N 1/20

US CL : 530/350; 536/23.1; 424/184.1; 435/325, 252.3

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350; 536/23.1; 424/184.1; 435/325, 252.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

search terms: secreted proteins, DNA, proteins, expression vectors

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,536,637 A (JACOBS) 16 June 1996, see entire document.	1-38
Y,E	US 5,770,209 A (GROTENDORST et al) 23 June 1998, see entire document.	1-38
Y	US 4,798,885 A (MASON et al) 17 January 1989, see entire document.	1-38
Y,E	US 5,773,586 A (GOSPODAROWICZ et al) 30 June 1998, see entire document.	1-38
Y,E	US 5,712,116 A (JACOBS) 27 June 1998, see entire document.	1-38
X,P	US 5,708,157 A (JACOBS et al) 13 January 1998, see entire document.	1-38

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

02 SEPTEMBER 1998

Date of mailing of the international search report

16 OCT 1998

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12516

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,E	US 5,792,628 A (BOWMAN) 11 August 1998, see entire document.	1-38
X,P	US 5,707,829 A (JACOBS et al) 13 January 1998, see entire document.	1-38

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